20 YEARS OF IIMCB

ANNUAL REPORT 2018

International Institute of Molecular and Cell Biology in Warsaw

Director
Marta Miączyńska

Deputy Director for Science
Jacek Jaworski

Deputy Director for Development
Urszula Białek-Wyrzykowska

Deputy Director for Operations
Anna Zolnik

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Photos by **Kryspin Andrzejewski** (pages 3, 4, 8, 9, 14, 15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 42, 43, 46, 47, 51, 55, 57, 59, 63), **Michał Bazała** (front cover picture, pages 11, 61, 62, 80-bottom), **Tomasz Bielecki** (page 50), **Daria Goś** (pages 60, 80-top, 91), **Marcin Zaręba/Polish-Swiss Research Programme** (back cover picture)

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Directors

Jacek Kuźnicki

Director (until 14.12.2018)

Marta Miączyńska

Director (since 15.12.2018)

Jacek Jaworski

Deputy Director for Science

Urszula Białek-Wyrzykowska

Deputy Director for Development

Anna Zolnik

Deputy Director for Operations

Hanna Iwaniukowicz

Deputy Director for Finance

Director's note

The year 2018 marked a time of transition for the International Institute of Molecular and Cell Biology in Warsaw and for the overall academic system in Poland. On December 15, 2018, I began my term as Director of IIMCB. I assumed the duties of Prof. Jacek Kuźnicki, who had been in charge of IIMCB for 20 years. It is my great honor and an immense responsibility to now head the institution that has become a benchmark of excellence in Polish science. The success of IIMCB has resulted from the hard work of tremendous and highly motivated individuals, both scientists and administrative personnel, united under the guidance of their visionary and courageous Director. On behalf of all present and past coworkers at IIMCB, I would like to thank Prof. Kuźnicki for his relentless efforts and steadfast dedication to the greater good of the Institute. Owing to his perseverance, the Institute has scientific and administrative staff of exceptional quality, a flat structure, and crucially a team spirit among all who work at IIMCB. These features have formed a solid foundation for our further development. I would also like to personally thank Prof. Kuźnicki for his support during my past 14 years at the Institute and for his openness and helpfulness in preparing me for my new duties.

The word *transition* means a movement or an evolution from one stage to another. In my view, it reflects well the current phase in the life of IIMCB, which has reached full maturity as an institution. The 20th Anniversary Symposium that took place on May 17, 2018, reminded us about IIMCB's beginning and early years. This joyful celebration and reunion provided a great opportunity to reflect on the process of growth and expansion of the Institute to its current size of 9 on-site research groups (with an additional group that is located in Poznań) and 220 coworkers. As a mature albeit still relatively young institution, IIMCB is now ready for new challenges. To define concrete goals that lie ahead, the directorship and all lab leaders convened for a retreat at the end of 2018. I am grateful to my colleagues for their creative contributions to our debate about the present and future of IIMCB. As a result of this collaborative effort, we reformulated the mission statement of the IIMCB:

"We support ambitious scientists of any nationality, driven by passion to pursue frontier research that aims to make a difference for society. We follow the principles of scientific freedom, integrity, and responsibility. We help researchers develop their careers through training and mentoring at all levels, and we encourage collaborations among them. We provide efficient administrative support that enables scientists to focus on their research."

Based on this mission statement, we identified several specific goals for the coming years that fall into three categories: scientific quality, institutional development and partnerships, and organizational culture. I would like to mention a few key aspects of these goals. With regard to scientific quality, we aim to make important scientific discoveries and report them in high-quality publications. We seek to achieve international recognition among the best research institutions in Europe and worldwide. To continue our institutional development, we will strive to obtain a larger building and reach a critical mass of ~20 research groups with complementary expertise, supported by professional state-of-the-art core facilities. While we wait for final funding decisions of Polish authorities, we have already begun preparing a concept for a new building that should both meet our current needs and provide flexibility for future growth and expansion into novel scientific and technological areas. We are also committed to our goals within the realm of organizational culture. We wish to give every staff member a sense of a joint mission and shared responsibility, based on a clear institutional structure, transparent regulations, and effective internal procedures. Equally important is to support collegiality and collaboration at all levels of the Institute and foster a professional and friendly work atmosphere.

These ambitious goals will be the leitmotif of my directorship. I will devote all my efforts to achieve them, as I promised during meetings with all IIMCB staff at the beginning of my term. I also asked for the support of every single coworker in realizing our mission. I am deeply convinced that together we will make a successful transition to the next challenging phase of IIMCB's development.

Finally, the academic system in Poland is also currently undergoing a transition. In October 2018, the new Law on Higher Education and Science (the so-called Constitution for Science or Act 2.0) went into force, although the implementation of some detailed orders is still pending. This new bill primarily affects universities, but it also impacts other aspects of the Polish science system, including rules for the evaluation and financing of research or doctoral education. Its overarching aim is to increase the excellence, competitiveness, and internationalization of science in Poland. At IIMCB, we welcome such efforts, which are entirely in line with our mission. Indeed, several of our lab leaders have been involved in preparing and implementing the current reform. We hope that the ongoing changes will gradually transform the academic landscape in Poland and help the best scientists unlock their full potential, curiosity, and creativity toward making important discoveries. In this spirit, IIMCB will always strive to make its mark through seminal discoveries that contribute to the world's overall scientific knowledge.

Warsaw, March 2019

Marta Miączyńska

International Advisory Board

International Advisory Board meeting, 18.05.2018, IIMCB, Warsaw, Poland

2018-2021 TERM

Thomas Braun Max Planck Institute for Heart and Lung Research, Germany

Bernd Bukau University of Heidelberg, Germany

Jo Bury Vlaams Instituut voor Biotechnologie, Belgium

Walter Chazin *(Chair)* Vanderbilt University, USA

Aaron Ciechanover Technion - Israel Institute of Technology, Israel

Urszula Hibner Institut de Génétique Moléculaire de Montpellier, France

Artur Jarmołowski Adam Mickiewicz University, Poland

Peter Sicinski Harvard Medical School, USA

Lilianna Solnica-Krezel Washington University School of Medicine, USA

Anne Spang University of Basel, Switzerland

Angelo Azzi *(Permanent Advisor)* Tufts University, USA

Martiale G. Zebaze Kana *(UNESCO Representative)* Division of Science Policy and Capacity Building, Natural Sciences Sector, UNESCO

Organizational structure

HR Excellence in Research

HR EXCELLENCE IN RESEARCH

Since 2013, the International Institute of Molecular and Cell Biology in Warsaw has been a holder of the **HR Excellence in Research logo**. This prestigious recognition acknowledges IIMCB as an attractive place for researchers to work and develop their careers. IIMCB received the third highest honor in Poland after the Foundation for Polish Science and Nencki Institute of Experimental Biology Polish Academy of Sciences (PAS).

The **HR Excellence in Research award** obligates IIMCB to continue improving human resources (HR) strategies with the principles set forth in the European Charter for Researchers and Code of Conduct for the Recruitment of Researchers (Charter & Code).

NEW HR WORKING GROUP CONSTITUTED OCT. 17, 2018

Agnieszka Faliszewska, HR Group Leader,
Prof. Jacek Jaworski, representing Directors and Lab Leaders,
Dr. Małgorzata Figiel, representing Postdoctoral Fellows,
Dr. Elżbieta Purta, representing Researchers,
Gabriela Jędruszewska, representing PhD Students,
Katarzyna Fiedorowicz, Head of Human Resources Unit,
Katarzyna Marszałek, Scientific Coordination Specialist,
Dorota Libiszowska, Head of Grants Office,
Daria Goś, PR Specialist.

IIMCB HR UNIT IN THE ACTION

In 2018 the in-house HR Unit went through the groundbreaking changes. With the support of the **funding from the EU H2020 MOSaIC project** it grew in number of personnel and activities – both for the proficient implementation of EU Charter & Code principles in our community.

The Institute employed **Katarzyna Fiedorowicz**, who now leads the HR team. Its seven members are responsible for: recruitment, payroll, career development and training, support to foreign employees, mediation/conflict resolution, and gender issues. We believe that systematic development of all these activities will help us cultivate a multinational, friendly, and stimulating environment that will attract the highest caliber of research scientists.

- New internal regulations

HR Unit introduced new internal legislation on: Organisational, Employee remuneration and Workplace rules. The purpose of preparing these Regulations is to create, unify and formalize the activities of the organization, oriented on scientific development and improving the quality of work of all employees.

- Open, transparent, and merit-based recruitment at IIMCB

HR Unit supports scientists in recruitment processes on systematic basis. They also prepared new guidelines on recruitment rules, prepared templates for a number of required documents, such as recruitment protocols or request for employment at IIMCB.

- Assistance to foreign employees in formalities during their stay in Poland

HR Unit supports IIMCB foreign employees from recruitment to employment. This includes arrangements for issuing visas, stay and work permits, medical visits, and housing arrangements.

CAREER DEVELOPMENT EVENTS

Workshop with the experts from the MSD Data Management Center departments on Clinical Trials and Pharmacovigilance, February 1, 2018. MSD experts gave presentations on company's activities and initiatives, e.g., MSD Foundation for Women's Health.

Lunches for young staff with external speakers invited to IIMCB for Institute's open seminars. IIMCB organized nine lunches. These activities are greatly appreciated by PhD students and postdoctoral researchers because they create a tremendous opportunity to discuss career ideas with foreign researchers who hold high esteem in the scientific world.

20th Anniversary of IIMCB

On May 17, 2018, we celebrated 20 years of the International Institute of Molecular and Cell Biology in Warsaw. On this occasion, IIMCB organized an international research symposium for present and past employees of the Institute and invited guests, followed by a celebratory dinner.

WE WERE DELIGHTED TO LISTEN TO LECTURES OF OUTSTANDING SPEAKERS

- **Anne Spang**, Biozentrum, University of Basel, Switzerland
  Compartmentation - modes of intracellular organization
- **Walter Chazin**, Vanderbilt University, USA
  Pushing the Horizon of Structural Biology
- **Lilianna Solnica-Krezel**, Washington University, USA
  Regulation of microtubule cytoskeleton by an atypical cadherin Dachsous
- **Aaron Ciechanover**, Technion - Israel Institute of Technology, Israel
  The ubiquitin proteolytic system: from basic mechanisms through human diseases and into drug targeting

THE EVENT WAS AN OPPORTUNITY TO RECALL THE HISTORY OF IIMCB, WITH PRESENTATIONS BY

- **Federico Mayor** (video broadcast), former Director General of UNESCO
- **Angelo Azzi**, first official Director of the Institute
- **Jerzy Duszyński**, President of the Polish Academy of Sciences
- **Michał Kleiber**, Polish Committee for UNESCO
- **Jacek Kuźnicki**, IIMCB Director from 2001 to 2018, presented the Institute's activities over the past 20 years

SHORT RETROSPECTIVE

An international agreement that established IIMCB was signed in May 1995 by Prof. Federico Mayor, UNESCO's Director General, and Prof. Aleksander Łuczak, Poland's Deputy Prime Minister. At the same time, the Polish Parliament and President ratified the May 1995 agreement. The appropriate legal foundation for the operations of IIMCB was finally created by the Parliamentary bill of June 26, 1997. Until that time, the Polish legal system had been unable to accommodate scientific institutions of international standing. Prof. Angelo Azzi was formally appointed as Director of the Institute, with deputies Prof. Jacek Kuźnicki (Acting Director) and Prof. Michał Witt (Scientific Director). On January 1, 1999, the International Institute of Molecular and Cell Biology in Warsaw began its independent existence.

THE FOLLOWING RESEARCH LABORATORIES WERE CREATED

- **Molecular Immunology** (1999-2004), headed by Jarosław Dastych
- **Molecular Biology** (2000-2016), headed by Maciej Żylicz
- **Bioinformatics** (2000-2002), headed by Leszek Rychlewski
- **Neurobiology** (2000-2003), headed by Michał Hetman
- **Neurodegeneration** (2001-present), headed by Jacek Kuźnicki
- **Biomodelling** (2002-2010), headed by Sławomir Filipek
- **Bioinformatics and Protein Engineering** (2002-present), headed by Janusz M. Bujnicki
- **Cell Biology** (2005-present), headed by Marta Miączyńska
- **Molecular and Cellular Neurobiology** (2005-present), headed by Jacek Jaworski
- **Cell Cortex Mechanics MPG/PAS** (2006-2012), headed by Ewa Paluch
- **Protein Structure** (2008-present), headed by Marcin Nowotny
- **Mitochondrial Biogenesis** (2009-2017), headed by Agnieszka Chacińska
- **Structural Biology** (2011-present), headed by Matthias Bochtler
- **Zebrafish Developmental Genomics MPG/IIMCB** (2014-present), headed by Cecilia L. Winata
- **Biomolecular Interactions and Transport AMU/IIMCB** (2016-present), headed by Jan Brezovsky
- **Iron Homeostasis** (2017-present), headed by Katarzyna Mleczko-Sanecka
- **Protein Metabolism in Development and Aging** (2017-present), headed by Wojciech Pokrzywa

Over the years, IIMCB has established a broad foundation for supporting basic and translational research and a rich environment for scientists who employ cutting-edge techniques. This has provided unique opportunities for cross-fertilization and collaboration. High-quality science and high research standards remain our trademark.

IIMCB Anniversary Symposium

Anne Spang, Biozentrum, University of Basel, Switzerland

Aaron Ciechanover, Technion - Israel Institute of Technology, Israel

Walter Chazin, Vanderbilt University, USA

Federico Mayor (video broadcast), former Director General of UNESCO

Lilianna Solnica-Krezel, Washington University, USA

Angelo Azzi, first official Director of the Institute

Jerzy Duszyński, President of the Polish Academy of Sciences

Michał Kleiber, Polish Committee for UNESCO

Jacek Kuźnicki, IIMCB Director from 2001 to 2018

Statuette presented to Jacek Kuźnicki

Anniversary lecture

Description of IIMCB's Activities

The International Institute of Molecular and Cell Biology in Warsaw is an independent basic research institute in the field of life sciences, holding the highest scientific category (A+) based on a parametric evaluation of research entities in Poland that is conducted by the Ministry of Science and Higher Education. For over 20 years, IIMCB has been internationally recognized for its fundamental biology research.

Our research groups address fundamental biological questions. Since IIMCB was established, scientists at the Institute have investigated important issues in such research areas as molecular and cellular biology, neurobiology, cancer biology, structural biology, bioinformatics, computer modeling, iron homeostasis, developmental genomics (zebrafish model), aging, and neurodegeneration. Nine high-profile research groups and a partner laboratory comprise the present structure of IIMCB:

- **Laboratory of Structural Biology**, headed by Matthias Bochtler
- **Laboratory of Bioinformatics and Protein Engineering**, headed by Janusz M. Bujnicki
- **Laboratory of Molecular and Cellular Neurobiology**, headed by Jacek Jaworski
- **Laboratory of Neurodegeneration**, headed by Jacek Kuźnicki
- **Laboratory of Cell Biology**, headed by Marta Miączyńska
- **Laboratory of Iron Homeostasis**, headed by Katarzyna Mleczko-Sanecka
- **Laboratory of Protein Structure**, headed by Marcin Nowotny
- **Laboratory of Protein Metabolism in Development and Aging**, headed by Wojciech Pokrzywa
- **Laboratory of Zebrafish Developmental Genomics**, headed by Cecilia L. Winata
- **Laboratory of Biomolecular Interactions and Transport AMU/IIMCB** located in Poznań, headed by Jan Brezovsky

IIMCB is directly subordinate to the President of the Polish Academy of Sciences (PAS), who supervises the organization and activities of the Institute. The President of PAS nominates members of the International Advisory Board and the Institute's Director. IIMCB occupies a building that was loaned to it by PAS. An important link between the Institute and the President of PAS is the 2nd Department of Biological Sciences of PAS, to which the Institute belongs together with 19 PAS institutes.

Scientists at IIMCB implement the latest methods and equipment in molecular biology, genetics, imaging, biochemistry, and structural biology using a vast array of model systems. This is achieved through the use of state-of-the-art core facilities that are available to all research groups at IIMCB. Research at IIMCB is supported by an annual statutory subsidy (3.7M EUR) from the Ministry of Science and Higher Education and budgetary subsidy (0.3M EUR) from PAS. The Institute's scientists obtained ~5M EUR from competitive sources (numerous grants from both foreign and domestic sources) in 2018. IIMCB performs innovative research at the highest level. In 2018, our scientists published 65 papers in international peer-reviewed journals. From 2000 to 2018, IIMCB scientists published 913 papers and received 300 grants (> 66.5M EUR) from external international and national sources. These grants include 60 from foreign funding institutions, such as the European Commission within the 5-7 Framework Programmes and Horizon 2020 (with 3 ERC), EMBO, HHMI, Wellcome Trust, Polish-Norwegian Research Fund, Polish-Swiss Research Programme, Max Planck Society, National Institutes of Health, and Deutsche Forschungsgemeinschaft. We also received 240 grants from EU Structural Funds, Polish funding agencies, and the Ministry for Science and Higher Education.

Currently, IIMCB comprises 180 employees, including 64 researchers, 44 PhD students, 39 technicians and 40 administration. Additionally, we have 40 contractors and volunteers. Many alumni of IIMCB hold positions in renowned universities or the public and private sectors. Seven of the 10 current Lab Leaders are Poles who returned to Poland after postdoctoral training at leading European and American research centers. The other three Lab Leaders are from Germany, Singapore, and Czech Republic. In total, 22% of IIMCB researchers are foreigners, representing eight nationalities. This creates a multinational and multicultural character of the Institute. English is the official language of communication and is used for correspondence, seminars, and meetings.

The international character of IIMCB is strongly echoed by all aspects of its functioning. All positions of laboratory leaders are filled through open international competitions, and candidates are selected by the International Advisory Board (IAB), a body that is unique to Polish research institutions. The IAB also consults on the steering and functioning of the Institute and meets with IIMCB researchers every year to discuss the quality, significance, and main focus of research that is conducted at the Institute. The members of the IAB are recognized scientists and science managers from the world's top research institutes (see page 4).

IIMCB has close scientific collaborations with world-renowned foreign research centers, such as the Max Planck Society (MPG). Under this strategic partnership, four laboratories were established with dual MPG and IIMCB affiliations: two laboratories at IIMCB (Prof. Bochtler's Laboratory of Structural Biology MPG/PAS and Dr. Winata's Laboratory of Developmental Zebrafish Genomics Max Planck/IIMCB) and two laboratories at MPG Institutes (Dr. Paluch's Laboratory of Cell Cortex Mechanics MPG/PAS located at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden [2006-2012] and Dr. Potente's Laboratory of Angiogenesis and Metabolism at the Max-Planck Institute for Heart and Lung Research in Bad Nauheim). The Institute also cooperates with national research centers, including the Intercollegiate Faculty of Biotechnology at the University of Gdańsk/Medical University of Gdańsk, Museum and Institute of Zoology PAS in Warsaw, and Institute of Molecular Biology and Biotechnology at Adam Mickiewicz University (AMU) in Poznań. Under this framework of cooperation, the Laboratory of Biomolecular Interactions and Transport AMU/IIMCB in Poznań was created (see page 50). In addition to institutional agreements, IIMCB research groups develop individual international collaborations through common grants, regular contacts, exchange visits, and systematically organized open seminars given by outstanding invited speakers from all over the world.

IIMCB also actively works to commercialize the results of research and inventions with high application potential. Measures that are implemented by IIMCB to commercialize its inventions and serve as a resource for industrial partners are continually adapted to scientific output and the needs and expectations of commercial partners. The commercialization of IIMCB inventions and technologies in life sciences, biotechnology, biomedicine, and bioinformatics is now run

by Biotech Innovations Ltd, an external entity that was set up by the Institute. Biotech Innovations is a special-purpose vehicle that is funded by IIMCB and committed to turning scientific progress into marketable products and technologies and returning income to the inventors and IIMCB to support further research activities. Because of the specificity of projects, Biotech Innovations develops and implements individual strategies for introducing products and services to the market. Among the more advanced projects are the following:

Auresine - a technology for the highly selective elimination of staphylococci bacteria using the Auresine enzyme. This technology is protected by a national and international patent. Two license agreements and a distribution agreement with Merck (Sigma Aldrich) were signed to ensure international product distribution. www.auresine.com

Futurenzymes - a spin-off company that is based on patented technology with potential significance in medical diagnosis and genetic engineering using enzymes that specifically cut double-stranded RNA molecules. www.futurenzymes.com

Joint projects are implemented at the Institute (on the basis of offering services or scientific cooperation) with major Polish biotechnology and pharmaceutical companies. IIMCB strongly collaborates with pharmaceutical and biotechnology companies, such as OncoArendi Therapeutics, A&A Biotechnology, Selvita, Polfa Warszawa, Adamed, Over Group, CelonPharma, UbiQ Bio, and IONIS, to develop new therapies in oncology and neurology and biotechnological products. The IIMCB Structural Biology Center began its activities in 2015. ProBiostructures (probiostructures.com) is a dedicated commercial laboratory whose mission is to harness the scientific excellence of IIMCB scientists to support drug discovery for the treatment of diseases. ProBiostructures specializes in consulting and providing services in structural biology, namely a complete range of protein X-ray crystallography research called "gene to structure."

In line with it's mission, the Institute also supports social initiatives that serve groups of patients with particular diseases. It has fostered two patient support organizations:

Polish Association Supporting People with Inflammatory Bowel Disease "J-elita" (2005-present), which brings together families of patients with Crohn's disease and colitis.

Polish Ciliary Dyskinesia Society (2011-present), which was initiated and further supported under two FP7 projects: HEALTH-PROT (RegPot) and BESTCILIA (a collaborative project that focuses on better experimental screening and treatment for primary ciliary dyskinesia).

IIMCB is also engaged in science popularization initiatives to increase awareness and interest in the life sciences among the general public. The Center for Innovative Bioscience Education (BioCEN) is an initiative that is supported by IIMCB that regularly hosts workshops with hands-on experiments and is engaged in science popularization events, such as the Warsaw Science Festival, Polish Radio Science Picnic, and Researchers' Nights (see page 88). IIMCB also organizes popularization campaigns, such as "Be Healthy as a Fish" (see page 90), involving the education of primary school students. IIMCB also holds regular seminars for students and talented youth.

IIMCB Group picture, Annual Report Session 2018

2018 Best Papers Award

Pawlak M, **Kedzierska KZ**, **Migdal M**, Nahia KA, Ramilowski JA, Bugajski L, Hashimoto K, **Marconi A**, Piwocka K, Carninci P, **Winata CL**. Dynamics of cardiomyocyte transcriptome and chromatin landscape demarcates key events of heart development. ***Genome Res***. 2019 Mar;29(3):506-519

Toczydlowska-Socha D, **Zielinska MM**, **Kurkowska M**, **Astha**, **Almeida CF**, **Stefaniak F**, **Purta E**, **Bujnicki JM**. Human RNA cap1 methyltransferase CMTr1 cooperates with RNA helicase DHX15 to modify RNAs with highly structured 5' termini. ***Philos Trans R Soc Lond B Biol Sci***. 2018 Nov 5;373(1762). pii: 2018016

Firkowska M, **Macias M**, **Jaworski J**. ESCRT Proteins Control the Dendritic Morphology of Developing and Mature Hippocampal Neurons. ***Mol Neurobiol***. 2018 Nov 7. Epub ahead of print

Figiel M, Krepl M, Park S, Poznański J, **Skowronek K**, Gołąb A, Ha T, Šponer J, **Nowotny M**. Mechanism of polypurine tract primer generation by HIV-1 reverse transcriptase. ***J Biol Chem***. 2018 Jan 5;293(1):191-202

BEST PAPERS AWARD REGULATIONS

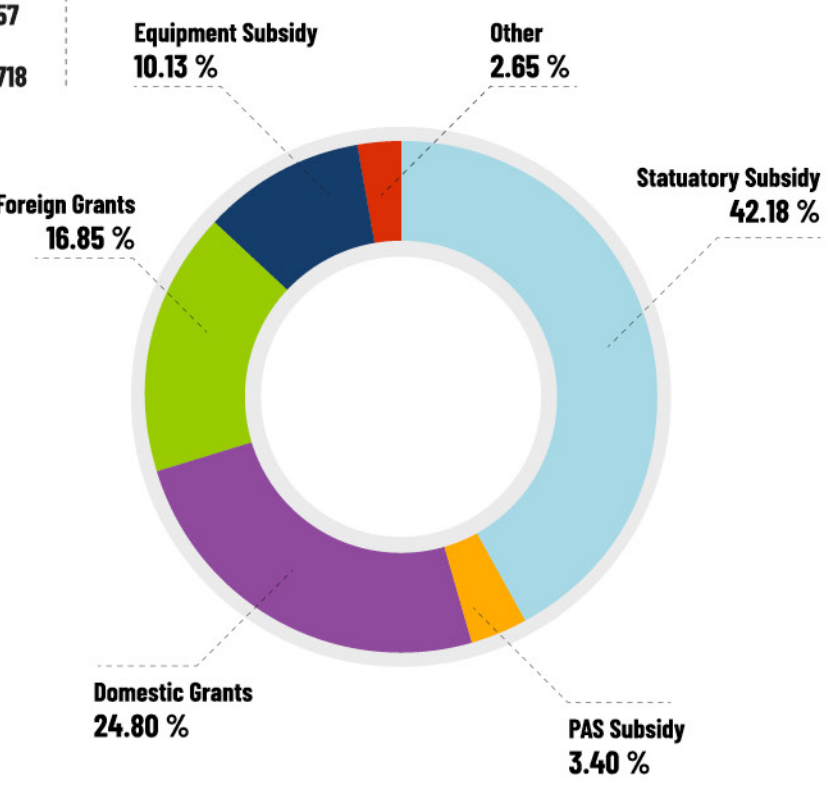
The best papers are selected by the Institute's Lab Leaders based on contents and significance, but not the bibliometric data. A full list and the pdf files of all the papers submitted for the Award (together with the supporting statements) are sent to each PI. They look through all of them and choose those which in their view deserve the Award. Of course they cannot vote for the papers from their own laboratory. The results are discussed during Lab Leaders meeting and the final winning papers' list is approved. The financial prizes are divided among the best papers' authors with IIMCB affiliation (listed in bold above).

Diversity of Funding

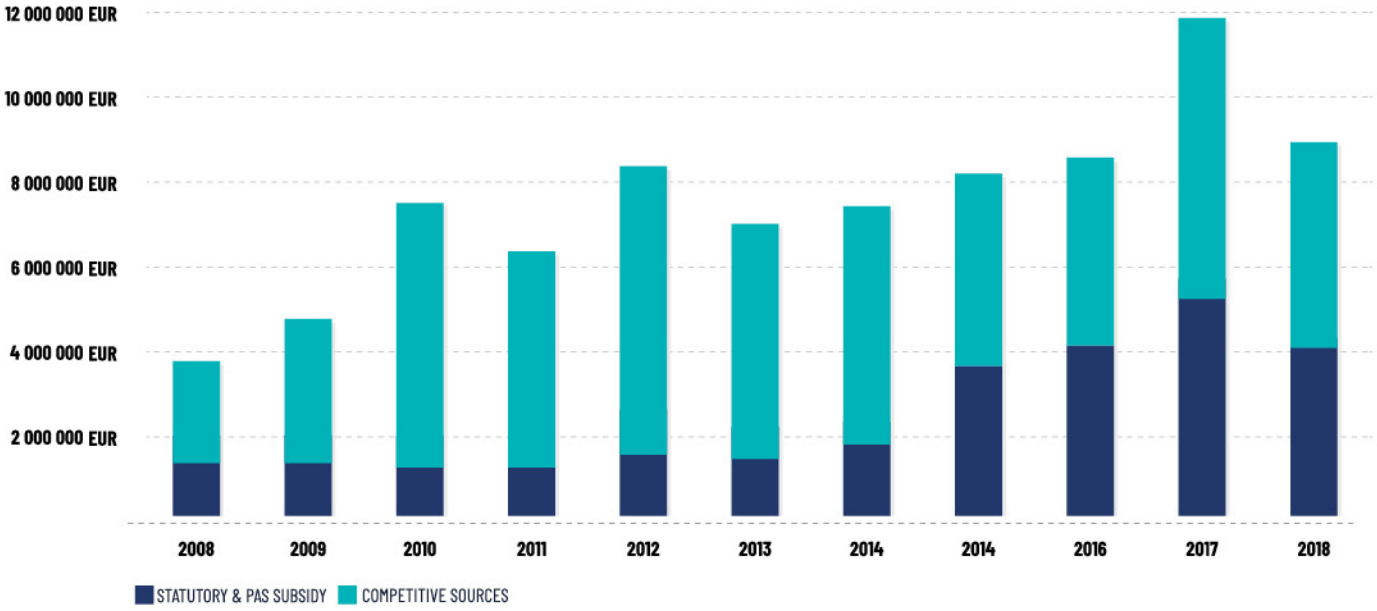
Sources of Funding in 2018

	PLN	EUR*
Statutory Subsidy	15 826 230	3 680 519
PAS Subsidy	1 274 000	296 279
Domestic Grants	9 304 238	2 163 776
Foreign Grants	6 320 857	1 469 967
Equipment Subsidy	3 800 000	883 721
Other	995 263	231 457
Total	37 520 588	8 725 718

*1 EUR - 4,3 @ 31st Dec'2018



Annual Income 2008-2018



Research Groups

Laboratory of Structural Biology

GROUP MEMBERS

Lab Leader
Matthias Bochtler, PhD, Professor

Senior Researcher
Honorata Czapińska, PhD

Postdoctoral Researchers
Humberto Fernandes, PhD (IBB PAS)
Anna Fricke, PhD
Thomas Fricke, PhD (until May 2018)
Joanna Krwawicz, PhD (until July 2018)
Małgorzata Perycz, PhD (part time, until May 2018)

PhD Students
Marlena Kisiała, MSc (IBB PAS, until February 2018)
Norbert Osiński, MSc
Michał Pastor, MSc (IBB PAS)
Dominik Rafalski, MSc
Anton Slyvka, MSc
Anna Stroynowska-Czerwińska, MSc
Katarzyna Szafran, MSc

Technician
Agnieszka Olszewska (part-time)

Laboratory-Administrative Partner
Małgorzata Perycz, PhD (part-time)

LAB LEADER

Matthias Bochtler, PhD, Professor

CURRICULUM VITAE

DEGREES

2009	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2006	DSc Habil, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland
1999	PhD in Biochemistry, Technical University of Munich, Germany
1995	MSc in Experimental Physics, Munich University, Germany

RESEARCH TRAINING

1996-1999	Research Assistant, Max Planck Institute of Biochemistry, Martinsried, Germany
1995-1996	Internship, Medical Microbiology, University of Regensburg, Germany
1992-1993	Guest Student, Cambridge University, United Kingdom
1990-1992	Studies in Physics, Munich University, Germany

PROFESSIONAL EMPLOYMENT

2011-Present	Professor, Head of Laboratory of Structural Biology, IIMCB, Warsaw, Poland and Laboratory of Genome Engineering, Institute of Biochemistry and Biophysics PAS, Warsaw, Poland
2007-2011	Part-time Director of Structural Biology, Cardiff University, United Kingdom
2001-2010	Head, Joint MPG-PAS Junior Research Group, IIMCB, Warsaw, Poland
2000	Patent training, Weickmann & Weickmann
1999-2000	Postdoctoral Fellow, Max Planck Institute of Biochemistry, Martinsried, Germany

HONORS, PRIZES, AND AWARDS

2018	TEAM, Foundation for Polish Science
2018	International Academic Partnerships Programme, Polish National Agency for Academic Exchange,
2018	DAINA, National Science Centre
2015	HARMONIA, National Science Centre
2014	OPUS, National Science Centre
2011	TEAM, Foundation for Polish Science
2005	Professor Stefan Pieńkowski Award
2004	EMBO/HHMI Young Investigator Award
2000	Crystal Award, Germany
1998	Crystal Award, Germany
1990-1992	Scholarship from Deutsche Studienstiftung and Bavarian State

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Filipek R, Firczuk M, Lipka M, Szczepanowski R, Kaus-Drobek M, Sokołowska M, Chojnowski G, Korza H, Wojciechowski M, Siwek W, Haniewicz P, Kazrani AA, Mierzejewska K.

SELECTED PUBLICATIONS

Publications in 2018

Tamulaitiene G, Manakova E, Jovaisaite V, Tamulaitis G, Grazulis S, **Bochtler M**, Siksnys V. Unique mechanism of target recognition by PfoI restriction endonuclease of the CCGG-family. *Nucleic Acids Res. 2019; 47(2):997-1010*

Kisiala M, Copelas A, **Czapinska H**, Xu S, **Bochtler M**. Crystal structure of the modification-dependent SRA-HNH endonuclease TagI. ***Nucleic Acids Res***. 2018; 46(19):10489-503

Czapinska H, **Kowalska M**, Zagorskaite E, Manakova E, **Slyvka A**, Xu SY, Siksnys V, Sasnauskas G, **Bochtler M.** Activity and structure of EcoKMcrA. ***Nucleic Acids Res***. 2018; 46(18):9829-41

Stroynowska-Czerwinska A, **Piasecka A**, **Bochtler M**. Specificity of MLL1 and TET3 CXXC domains towards naturally occurring cytosine modifications. ***Biochim Biophys Acta Gene Regul Mech***. 2018; 1861(12):1093-1101

Piasecka A, **Czapinska H**, Vielberg MT, **Szczepanowski RH**, Kiefersauer R, Reed S, Groll M, **Bochtler M**. The Y. bercovieri Anbu crystal structure sheds light on the evolution of highly (pseudo)symmetric multimers. ***J Mol Biol***. 2018; 430(5):611-627

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Szczepanowski RH, Carpenter MA, **Czapinska H**, Zaremba M, Tamulaitis G, Siksnys V, Bhagwat AS, **Bochtler M**. Central base pair flipping and discrimination by PspGI. ***Nucleic Acids Res***, 2008; 36(19):6109-17

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Kaus-Drobek M, **Czapinska H**, **Sokolowska M**, Tamulaitis G, **Szczepanowski RH**, Urbanke C, Siksnys V, **Bochtler M**. Restriction endonuclease MvaI is a monomer that recognizes its target sequence asymmetrically. ***Nucleic Acids Res***, 2007; 35(6):2035-46

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DESCRIPTION OF CURRENT RESEARCH

Our group is interested in DNA modifications, their specific recognition by proteins, and the machinery that is involved in altering them. DNA methylation is a single-step reaction. In contrast, DNA demethylation proceeds in several steps. Methylated cytosines are first oxidized by ten eleven translocation (TET) enzymes and then excised by base excision repair or possibly other DNA repair pathways (for review, see Bochtler et al., *Bioessays*, 2017).

STRUCTURAL BIOLOGY PROJECTS

In 2018, the group has completed several projects that revolve around the specific recognition of nucleic acids by proteins. In particular, we have looked at mechanisms of semi-degenerate recognition by nucleotide flipping and mechanisms of the recognition of modified DNA. This resulted in three publications in Nucleic Acid Research in 2018, which are briefly summarized here.

In the Tamulaitiene et al. paper, we report the class of so-called "CCGG" restriction endonucleases that can be divided into two groups. Some of them recognize uninterrupted CCGG, and others are specific to the CCNGG, CCWGG, or CCSGG sequence (where N stands for any base, W stands for A or T, and S stands for G or C), with possible additional specificity for flanking bases. Despite very low sequence similarity, the CCGG enzymes are evolutionarily related and adopt similar structures. As we originally discovered almost a decade ago, the "inserted" central base pair is always flipped in this class of enzymes, making it possible to compress semi-palindromic DNA to the size of the palindromic congener. In the Tamulaitiene et al. paper, we report crystal structures of the 5'-T|CCNGGA-3' specific PfoI endonuclease, which was expected to be similar to other pseudo-palindrome cutters but that surprisingly recognizes DNA rather differently.

In the Kisiala et al. paper, we report the first crystal structure of an SRA-HNH endonuclease. The structure of the TagI enzyme shows that it interacts with the modified cytosine base through a nucleotide flipping mechanism (Fig. 1). The structure reveals the bases of discrimination between cytosine and

5glucosylhydroxymethylcytosine and between 5-methylcytosine and 5hydroxymethylcytosine. Apart from informing about mechanistic aspects of modified cytosine recognition, the structure suggests design rules to create better SRA-HNH endonuclease substrates.

In the Czapinska et al. paper, we characterize the EcoKMcrA enzyme, a classic methylcytosine and hydroxymethylcytosine specific restriction endonuclease (Fig. 2). The enzyme has been studied for over 50 years but has remained mechanistically enigmatic, partially because no *in vitro* endonuclease activity could be demonstrated. We solved the crystal structure of EcoKMcrA and revealed a two-domain architecture that is reminiscent of SRA-HNH endonucleases but with an N-terminal domain that is evolutionarily unrelated to SRA domains and interacts with the modified DNA differently. SRA-HNH endonucleases flip the modified base, but biochemical assays suggest that EcoKMcrA interacts with the modified bases in the context of double-stranded DNA.

BIOCHEMICAL/GENETIC PROJECTS

We are continuing our work with Prof. Tomasz Jurkowski on the sequence and locus specificity of TET dioxygenases that are involved in 5-methylcytosine oxidation und ultimately replacement by unmodified cytosines. In 2018, we grew crystals of TET2 with different target sequences and attempted to study these complexes by electron microscopy but unfortunately without much success. We are currently attempting to complement the crystallographic data with atomic force microscopy imaging.

We are also continuing our work on links between DNA reprogramming and DNA repair. Some of our experiments, such as those on the role of NEIL1 and TDG in the excision of oxidized 5-methylcytosine bases, are consistent with the general paradigm that DNA reprogramming co-opts DNA repair. However, based on much circumstantial evidence and the work of others, we suspect that the converse may also be true and that DNA repair may use intermediates that are normally associated with reprogramming. We will test this hypothesis both biochemically and bioinformatically.

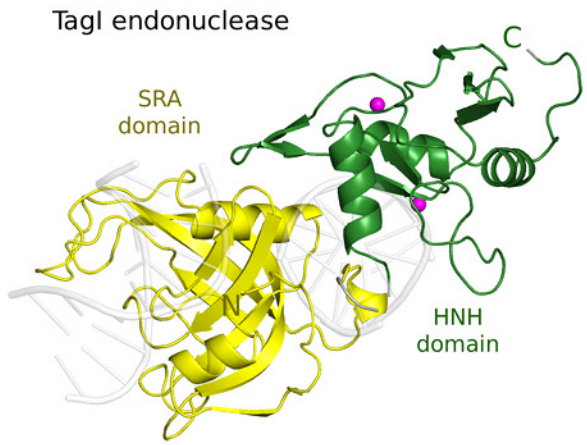

Fig. 1 Schematic view of the crystal structure of modification specific TagI restriction endonuclease. The enzyme is composed of two domains: a modification sensitive SRA domain and a catalytic domain of the HNH type. Only the protein was present in the crystal, the DNA is modelled based on structure similarity to UHRF1 (for the SRA domain) and Hpy99I (for the nuclease domain). The enzyme dimerizes through the nuclease domains but only a single protomer is shown in the figure for clarity.

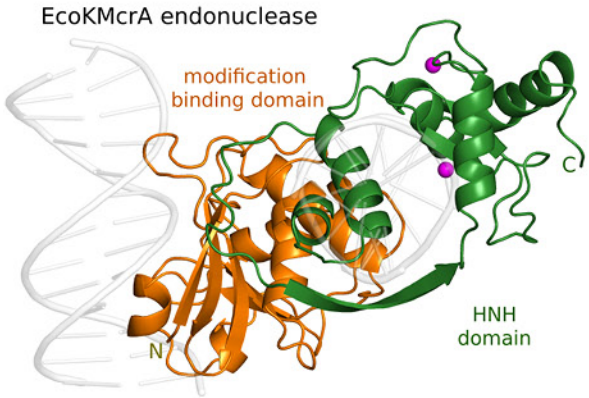

Fig. 2 Crystal structure of the 5-(hydroxymethyl)cytosine specific EcoKMcrA restriction endonuclease. The nuclease domain of EcoKMcrA is structurally very similar to the one of TagI. However, despite similar modification dependence, its N-terminal domain is unrelated to the SRA domains and is likely to recognize the modifications in a novel way. Only the protein was present in the crystal, the DNA is modelled based on the Hpy99I-DNA complex for the nuclease domain and very roughly positioned based on a very distantly similarity to I-DmoI homing endonuclease. The enzyme forms dimer but only a single protomer is shown.

Laboratory of Bioinformatics and Protein Engineering

GROUP MEMBERS

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Senior Scientists
Elżbieta Purta, PhD
Filip Stefaniak, PhD

Researcher
Michał Boniecki, PhD

Postdoctoral Researchers
Lucyna Budźko, PhD (until December 2018)
Nithin Chandran, PhD
Justyna Czarnecka, PhD (until July 2018)
Pritha Ghosh, PhD
Marcin Magnus, PhD (until March 2018)
Almudena Ponce Salvatierra (since October 2018)
Radosław Pluta, PhD (until June 2018)
Tomasz Wirecki, PhD

PhD Students
Astha, MSc (until December 2018)
Błażej Bagiński, MSc (until November 2018)
Pietro Boccaletto, MSc
Chinju John, MSc (until March 2018)
Magdalena Orłowska, MSc
Diana Toczydłowska, MSc (until December 2018)
Adriana Żyła, MSc (until April 2018)
Iswarya Pandara Nayaka PJ
Sachin Gadakh

Research Technicians
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Małgorzata Kurkowska, MSc
Katarzyna Merdas, MSc (until December 2018)
Sunandan Mukherjee, PhD
Ewa Skowronek, PhD
Magdalena Sroka, MSc (until August 2018)

MSc Students
Joanna Broniarek, BSc (until July 2018)
Dharm Skandh Jain, BSc

Technician
Iwona Ptasiewicz (part-time)

Laboratory-Administrative Partner
Agnieszka Faliszewska, MSc (until April 2018)
Katarzyna Grzelak, MSc (since May 2018)

LAB LEADER

Janusz M. Bujnicki, PhD, Professor

CURRICULUM VITAE

DEGREES

2009	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2005	DSc Habil in Biochemistry, Institute of Biochemistry and Biophysics PAS, Warsaw, Poland
2001	PhD in Biology, University of Warsaw, Faculty of Biology, Poland
1998	MSc in Microbiology, University of Warsaw, Faculty of Biology, Poland

PROFESSIONAL EXPERIENCE

2002-Present	Professor, Head of Laboratory of Bioinformatics and Protein Engineering, IIMCB, Warsaw, Poland (100% appointment)
2006-Present	Associate Professor (extraordinarius) Bioinformatics Laboratory, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University, Poznań, Poland (currently 25% appointment)
2010-2011	Deputy Director, IIMCB (1 year rolling position)
2008	Visiting Professor, University of Tokyo, Japan (sabbatical)
2004-2006	Assistant Professor, Adam Mickiewicz University
2001	Visiting Scientist, National Center for Biotechnology Information, National Institutes of Health, Bethesda, Maryland, USA
1999-2002	Research Scientist, Bioinformatics Laboratory, IIMCB
1998-2000	Senior Research Assistant, Henry Ford Hospital, Detroit, Michigan, USA

SELECTED PROFESSIONAL AFFILIATIONS

Academia Europaea member (2018-Present)

EMBO member (2018-Present)

European Science Advisors Forum (member, 11.2017-Present)

Group of Chief Scientific Advisors within the European Commission's Scientific Advice Mechanism (2015-Present)

Scientific Policy Committee (2014-2018, chairman 04-09.2015 & 06-12.2016)

Scientific Committee of the Innovative Medicines Initiative (2013-2016)

Council of the National Science Congress (2016-2017)

Science Europe: Life, Environmental and Geo Sciences (LEGS) Scientific Committee (2013-2015)

Young Academy, Polish Academy of Sciences, AMU-PAS (2011-2016)

Polish Academy of Sciences, corresponding member (2016-Present)

Member: Polish Bioinformatics Society, PTBI (founding member, Vice-President 2007-2010, President 2011-2013), International Society for Computational Biology, RNA Society

Executive Editor, Nucleic Acids Research (2013-Present)

SELECTED AWARDS AND FELLOWSHIPS

2017	Award for Organizational Achievements, Ministry of Science and Higher Education
2016	Crystal Brussels Sprout – special award of the National Contact Point of the EU
2015	Jan Karol Parnas Award of the Polish Biochemical Society
2014	Award of the Polish National Research Center (NCN)
2014	Master Programme Award, Foundation for Polish Science
2014	Prime Minister's Award for outstanding scientific achievements
2014	Selected as one of "25 leaders for the next 25 years" by "Teraz Polska" magazine of the Polish Promotional Emblem Foundation
2014	Knight's Cross of the Order of Polonia Restituta
2014	Award in the Science category of the national plebiscite "Poles with Verve"
2012	Award for Outstanding Research Achievements, Ministry of Science and Higher Education
2010	ERC Starting Grant (2011-2015)
2009	Fellowship for Outstanding Young Scientists, Ministry of Science and Higher Education
2009	Award for Research Achievements, Ministry of Science and Higher Education
2006	Prime Minister Award for the habilitation thesis
2006	Young Researcher Award in Structural and Evolutionary Biology, Visegrad Group Academies of Sciences
2003,2004	Fellowship for Young Scientists, Foundation for Polish Science
2002-2005	EMBO/Howard Hughes Medical Institute Young Investigator Program Award
2002	Award of the Polish Genetics Society (best Polish genetics-related publication in 2002)
2001	Award of the Polish Biochemical Society and Sigma-Aldrich (best Polish publication on nucleic acid biochemistry in 2000)

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Żylicz-Stachula A, Chmiel A, Cymerman I, Czerwoniec A, Gajda M, Pawłowski M, Sasin-Kurowska J, Kosinski J, Obarska-Kosińska A, Pawlak S, Purta E, Tkaczuk K, Kosciński Ł, Rother M, Potrzebowski W, Korneta I, Puton T, Kasprzak J, Tuszyńska I, Kozłowski Ł, Werner M, Kamaszewska A, Philips A, Milanowska K, Piętal M, Matelska D, Majorek K, Domagalski M, Osinski T, Machnicka M, Magnus M, Szczepaniak K, Zielińska M, Astha, Foik I.

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Sweeney BA, Petrov AI, Burkov B, Finn RD, Bateman A, Szymanski M, Karlowski WM, Gorodkin J, Seemann SE, Cannone JJ, Gutell RR, Fey P, Basu S, Kay S, Cochrane G, Billis K, Emmert D, Marygold SJ, Huntley RP, Lovering RC, Frankish A, Chan PP, Lowe TM, Bruford E, Seal R, Vandesompele J, Volders PJ, Paraskevopoulou M, Ma L, Zhang Z, Griffiths-Jones S, **Bujnicki JM**, **Boccaletto P**, Blake JA, Bult CJ, Chen R, Zhao Y, Wood V, Rutherford K, Rivas E, Cole J, Lauledernkind SJF, Shimoyama M, Gillespie ME, Orlic-Milacic M, Kalvari I, Nawrocki E, Engel SR, Cherry JM, Team S, Berardini TZ, Hatzigeorgiou A, Karagkouni D, Howe K, Davis P, Dinger M, He S, Yoshihama M, Kenmochi N, Stadler PF, Williams KP. RNAcentral: a hub of information for non-coding RNA sequences. ***Nucleic Acids Res,*** 2019; 47:D221-D229

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Smietanski M, **Werner M**, **Purta E**, **Kaminska KH**, Stepinski J, Darzynkiewicz E, **Nowotny M**, **Bujnicki JM**. Structural analysis of human 2'-O-ribose methyltransferases involved in mRNA cap structure formation. ***Nat Commun***, 2014; 5:3004

Matelska D, **Purta E**, **Panek S**, **Boniecki MJ**, **Bujnicki JM**, **Dunin-Horkawicz S**. S6:S18 ribosomal protein complex interacts with a structural motif present in its own mRNA. ***RNA***, 2013; 19(10):1341-48

Pawlowski M, **Bogdanowicz A**, **Bujnicki JM**. QA-RecombineIt: a server for quality assessment and recombination of protein models. ***Nucleic Acids Res,*** 2013;41:W389-W397

Puton T, **Kozlowski L**, **Rother KM**, **Bujnicki JM**. CompaRNA: a server for continuous benchmarking of automated methods for RNA secondary structure prediction. ***Nucleic Acids Res***, 2013; 41(7):4307-23

Machnicka MA, **Milanowska K**, Osman Oglu O, **Purta E**, **Kurkowska M**, **Olchowik A**, **Januszewski W**, **Kalinowski S**, **Dunin-Horkawicz S**, **Rother KM**, Helm M, **Bujnicki JM**, Grosjean H. MODOMICS: a database of RNA modification pathways: 2012 update. ***Nucleic Acids Res***, 2013; 41(D1):D262-D267

Our group is involved in theoretical and experimental research on sequence structure-function relationships in proteins, nucleic acids, and macromolecular complexes. Theoretical research involves the development of computer software for the analysis of biological macromolecules. We are currently focusing on developing software for the structural prediction and modeling of RNA and RNA protein complexes. To date, we have developed and made publicly available one of the first methods for the automated comparative (template-based) modeling of three-dimensional (3D) RNA structures (ModeRNA; http://iimcb.genesilico.pl/moderna/) and a method for de novo (template-free) RNA structure modeling (SimRNA; http://genesilico.pl/software/stand-alone/simrna, also available as a web server at http://genesilico.pl/SimRNAweb). We also developed a method for predicting metal ion binding sites in RNA structures (MetalionRNA; http://metalionrna.genesilico.pl), a method for modeling RNA-ligand complexes (LigandRNA; http://ligandrna.genesilico.pl), and a method for predicting the structure of RNA-protein complexes (http://genesilico.pl/NPDock). Other methods for RNA bioinformatics include a method for the classification of contacts in RNA 3D structures (ClaRNA; http://iimcb.genesilico.pl/clarna/) and a method for the flexible superposition of RNA 3D structures and their fragments (SupeRNAlign; http://genesilico.pl/supernalign/). We also developed various databases, including a database of RNA modification pathways and enzymes (MODOMICS; http://modomics. genesilico.pl) and a database of RNA 3D motifs and their interactions (RNA Bricks; http://iimcb.genesilico.pl/rnabricks/).

Our suite of programs for the prediction and analysis of protein structures and macromolecular complexes includes the GeneSilico MetaServer (https://www.genesilico.pl/meta2/), methods for modeling large macromolecular complexes with the use of restraints that are derived from experimental data (PyRy3D, http://genesilico.pl/pyry3d/; MinkoFit3D, http://iimcb.genesilico.pl/minkofit3d/), and a method for discriminating models according to their agreement with experimental data (FILTREST3D; http://filtrest3d.genesilico.pl/). We also developed methods for predicting order/disorder in protein structures (http://iimcb.genesilico.pl/metadisorder/).

Our experimental research focuses on elucidating sequence structure-function relationships in proteins and nucleic acids using biophysics, biochemistry, molecular biology, and cell biology. We tightly integrate theoretical and experimental research. We often experimentally test functional and structural predictions for proteins and RNAs and their complexes using computational methods. For structural studies, we combine X-ray crystallography and low-resolution methods, such as small-angle X-ray scattering (SAXS), structure probing by chemical modification or crosslinking, mass spectrometry, circular dichroism, mutagenesis, etc. We also use experimental methods for protein engineering to obtain enzymes with new, useful features, particularly alterations of substrate specificity (e.g., nucleases that exhibit new substrate specificities).

RECENT HIGHLIGHTS

Human RNA cap1 methyltransferase CMTr1 cooperates with RNA helicase DHX15 to modify RNAs with highly structured 5′ termini

In higher eukaryotes, 5′ ends of all mRNAs and many non-coding RNAs, including long non-coding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs), and the majority of small nuclear RNAs (snRNAs) are modified by ribose 2′-*O*-methylation on the first transcribed nucleotide. This additional methylation enhances the translation of mRNA during oocyte maturation and facilitates the splicing of small nuclear RNAs. Beyond these functions, the cap1 structure is essential for non-self-discrimination of the innate immune response against foreign RNA. In humans, cap1 methylation occurs on all capped and polyadenylated RNA molecules, whereas only about half of these molecules contain cap2 methylation.

We have determined the crystal structures of the active CMTr1 catalytic domain in complex with a methyl group donor SAM and a capped 4 nt ribonucleotide (m7GpppGAUC), thereby revealing the mechanism of CMTr1 interactions with the 5′ terminus of a capped RNA. The analysis of this structure shows the lack of contacts between the bases of the transcript (GAUC) and the CMTr1 protein, suggesting that substrate binding and methylation are sequence-independent. We found that CMTr1 indeed acts poorly on RNA substrates with an extensive secondary structure in the 5′ terminus. To methylate these targets efficiently, CMTr1 may require the secondary structure to be removed, which could be a task for an RNA helicase. Consistent with the potential requirement for help in removal of the secondary structure from the 5′ end of the RNA, we found that CMTr1 interacts strongly with an ATP-dependent RNA helicase, DHX15. Thus far, DHX15 and its yeast homologue Prp43 have been implicated in diverse cellular functions that involve RNA metabolism, including splicing and ribosome biogenesis, but not in RNA modification.

Interactions between Cmtr1 methyltransferase and DHX15 helicase are mediated by the G-patch domain. The CMTr1 variant that lacks the G-patch domain does not bind DHX15, and it also cannot be aided by DHX15 in the methylation of RNAs that contain strongly structured 5′ termini. This provides evidence of a G-patch-dependent interaction between CMTr1 and DHX15, which enables CMTr1 to efficiently methylate all types of capped substrates, regardless of their secondary structure. Based on the available data, we speculate that CMTr1 and DHX15 form a relatively stable complex, using the G-patch domain of CMTr1 and the OB-fold domain of DHX15, which can bind capped RNAs. The CMTr1 can either directly methylate the first transcribed nucleotide in RNAs with unstructured 5′ termini or use the help of a physically associated DHX15 protein to free the 5′-terminal region from base-pairing, thereby making it available for methylation.

RNA methylation has been found to influence RNA structure. In particular, m6A alters the local RNA structure and acts as a dynamic switch that can control the RNA structure-dependent accessibility of RNA binding motifs. 2′-*O*-methylation was also suggested to affect RNA folding and structural stability. We demonstrated a reverse functional relationship, in which the RNA secondary structure determines its own potential to be methylated. Discovery of the involvement of DHX15 in RNA methylation suggests that CMTr1 activity on structured substrates can be regulated to enable efficient modification. A publication reporting these findings (Toczydlowska-Socha et al., *Philos Trans R Soc Lond B Biol Sci*, 2018) has been awarded in the annual competition for the best publications from IIMCB.

New project: toward designing new RNA molecules with desired spatial shape and functionality

One of the fundamental challenges of biology and chemistry is to design molecules that form desired structures and perform desired functions. The computational design of RNA requires solving the so-called RNA inverse folding problem (i.e., given a target structure, identify one or more sequences that fold into that structure and do not fold into any other structure). Designing RNA sequences with specific folding properties and desired functions has already proven useful in numerous applications in such areas as the development of probes and sensors, molecular medicine, and material science. Nonetheless, RNA design is very difficult, especially for molecules with complex structures. In particular, few methods are available for designing RNA 3D structures, and they have severe restrictions. For example, they usually require a fixed RNA structural framework and only allow the RNA bases to change but keep the sequence length and shape of the RNA chain fixed.

To date, we developed a prototypical method, DesiRNA, that enables designing RNA oligomers and alternative structures. Our group has also developed an extension of our RNA 3D structure prediction method, SimRNA, which can "mutate" the RNA sequence during 3D folding simulations. Together, these new methods can overcome current limitations.

Recently, a new grant project entitled, "Development of new methods for designing RNA molecules that fold into desired spatial structures and their use for the development of new functional RNAs and for prediction of noncoding RNAs in transcriptome sequences," was awarded within the OPUS program of the Polish National Science Centre (NCN). The main goal of this new project is to further develop our computational tools and combine them into a software package for designing RNAs that are composed of one or multiple strands and are able to switch between different 3D structures (including changes in global shape, patterns of canonical and non-canonical base pairs, and oligomeric states). The proposed program will provide a comprehensive tool for designing novel RNA molecules, and it will be tested in practice in various applications.

Laboratory of Molecular and Cellular Neurobiology

GROUP MEMBERS

Lab Leader
Jacek Jaworski, PhD, Professor

Senior Scientists
Ewa Liszewska, PhD
Matylda Macias, PhD (part-time)
Małgorzata Urbańska, PhD

Postdoctoral Researchers
Magdalena Błażejczyk, PhD
Agnieszka Brzozowska, PhD
Aleksandra Janusz-Kamińska, PhD
Bartosz Tarkowski, PhD (until September 2018)
Michalina Wężyk, PhD
Justyna Zmorzyńska, PhD

Junior Researchers
Katarzyna Banasiak, BSc (until July 2018)
Marcelina Firkowska, MSc
Magdalena Kędra, MSc
Alicja Kościelny, MSc
Kinga Kuchcińska, MSc
Hadi Mirzapour Delavar, MSc (until December 2018)
Magdalena Mlostek, MSc (since November 2018)
Katarzyna Rydz, MSc
Katarzyna Świtoń, MSc (until September 2018)
Aleksandra Tempes, MSc
Oliver Tkaczyk, MSc (since October 2018)
Jan Węsławski, MSc

Technician
Alina Zielińska, MSc

Laboratory-Administrative Partner
Marcelina Firkowska, MSc

LAB LEADER

Jacek Jaworski, PhD, Professor

CURRICULUM VITAE

DEGREES

2014	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2010	DSc Habil in Molecular Biology, Warsaw University, Poland
2001	PhD in Molecular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1996	MSc in Biology, Department of Genetics, Warsaw University, Poland

PROFESSIONAL EXPERIENCE

2018-present	Deputy Director for Science, IIMCB, Warsaw, Poland
2010-2013	Deputy Director,IIMCB, Warsaw, Poland
2005-Present	Professor, Head of Laboratory of Molecular and Cellular Neurobiology, IIMCB, Warsaw, Poland

RESEARCH TRAINING

2016	Research visit (3 weeks) with Prof. William Harris, Cambridge University, Cambridge, UK
2011	Research visit (2 weeks) with Dr. Carlo Sala, CNR Institute of Neuroscience & Instituto Neurologico Carlo Besta, Milan, Italy
2006	Research visit (1 month) with Dr. C.C. Hoogenraad, Erasmus Medical Center, Rotterdam, Holland
2002-2005	Postdoctoral Associate with Prof. Morgan Sheng, Picower Center for Learning and Memory, Massachusetts Institute of Technology and Howard Hughes Medical Institute, Cambridge, MA, USA
2000	Research training (1 month) with Dr. J. Guzowski, ARL Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, USA
1997-2001	Research training (7 months) with Prof. J. Mallet, Laboratoire de Genetique Moleculaire de la Neurotransmission et des Processus Neurodegeneratifs (LGN), UMR 9923, Centre National de la Recherche Scientifique, Paris, France
1996-2002	PhD student (until 2001) and Postdoctoral Associate (until May 2002) with Prof. L. Kaczmarek, Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1995-1996	Master's degree, Prof. P. Węgleński, Department of Genetics, Warsaw University, Poland

FELLOWSHIPS AND AWARDS

2018	TEAM, Foundation for Polish Science
2014	Master Programme Award, Foundation for Polish Science
2011	Prime Minister Award for habilitation thesis
2009	2nd Division (Biological Sciences) of Polish Academy of Sciences Award for series of publications on MMP9 (together with teams of Prof. Kaczmarek and Dr. Wilczyński)
2002	Prime Minister Award for PhD thesis
2001	START, Foundation for Polish Science (1 year scholarship)

MEMBERSHIP IN SCIENTIFIC SOCIETIES, ORGANIZATIONS, AND PANELS

2017	Vice President of Polish Neuroscience Society
2015	Warsaw Scientific Society, Corresponding Member
2015	Scientific Advisory Board to the Nencki Institute of Experimental Biology, PAS, Member
2011	Neurobiology Committee of the Polish Academy of Sciences, Member (terms 2011-2014; 2015-2018)

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Świech Ł, Malik A, Perycz M, Urbańska M, Skałecka A, Lipka J, Urbańska A.

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Publications in 2017-2019

Urbanska M, Kazmierska-Grebowska P, Kowalczyk T, Caban B, Nader K, Pijet B, Kalita K, **Gozdz A**, Devijvere H, Lechate B, Jaworski T, Grajkowska W, Sadowski K, Jozwiak S, Kotulska K, Konopacki J, Van Leuven F, van Vlieth E, Aronica E, **Jaworski J**. GSK3β activity alleviates epileptogenesis and limits GluA1 phosphorylation. ***EBioMedicine***, 2019; 39:377-387

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Jaworski J, Kalita K, Knapska E. c-Fos and neuronal plasticity: the aftermath of Kaczmarek's theory. ***Acta Neurobiol Exp***, 2018; 78(4):287-296

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Gozdz A, Nikolaienko O, **Urbanska M**, **Cymerman IA**, Sitkiewicz E, **Blazejczyk M**, Dadlez M, Bramham CR, **Jaworski J**. GSK3α and GSK3β Phosphorylate Arc and Regulate its Degradation. ***Front Mol Neurosci***, 2017; 10:192

Kononenko NL, Classen GA, Kuijpers M, Puchkov D, Maritzen T, **Tempes A**, **Malik AR**, **Skalecka A**, Bera S, **Jaworski J**, Haucke V. Retrograde transport of TrkB-containing autophagosomes via the adaptor AP-2 mediates neuronal complexity and prevents neurodegenretaion. ***Nat Commun,*** 2017; 8: 14819

de Hoz L, Gierej D, Lioudyno V, **Jaworski J**, **Blazejczyk M**, Cruces-Solís H, Beroun A, Lebitko T, Nikolaev T, Knapska E, Nelken I, Kaczmarek L. Blocking c-Fos Expression Reveals the Role of Auditory Cortex Plasticity in Sound Frequency Discrimination Learning. ***Cereb Cortex***, 2017; 1-11

Switon K, Kotulska K, **Janusz-Kaminska A**, **Zmorzynska J**, **Jaworski J**. Molecular neurobiology of mTOR. ***Neuroscience,*** 2017; 341:112-153

Blazejczyk M, **Macias M**, Korostynski M, **Firkowska M**, Piechota M, **Skalecka A**, **Tempes A**, **Koscielny A**, **Urbanska M**, Przewlocki R, **Jaworski J**. Kainic Acid Induces mTORC1-Dependent Expression of Elmo1 in Hippocampal Neurons. ***Mol Neurobiol***, 2017; 54(4):2562-78

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Other selected publications

Skalecka A, **Liszewska E**, Bilinski R, Gkogkas C, Khoutorsky A, **Malik AR**, Sonenberg N, **Jaworski J**. mTOR kinase is needed for the development and stabilization of dendritic arbors in newly born olfactory bulb neurons. ***Dev Neurobiol***, 2016; 76(12):1308-1327

Lipka J, Kapitein LC, **Jaworski J**, Hoogenraad CC. Microtubule-binding protein doublecortin-like kinase 1 (DCLK1) guides kinesin-3-mediated cargo transport to dendrites. ***EMBO J***, 2016; 35(3):302-318

Malik AR, **Liszewska E**, **Skalecka A**, **Urbanska M**, Iyer AM, **Swiech LJ**, **Perycz M**, **Parobczak K**, **Pietruszka P**, **Zarebska MM**, **Macias M**, Kotulska K, Borkowska J, Grajkowska W, Tyburczy ME, Jozwiak S, Kwiatkowski DJ, Aronica E, **Jaworski J**. Tuberous sclerosis complex neuropathology requires glutamate-cysteine ligase. ***Acta Neuropathol Commun***, 2015; 3:48

Malik AR, **Urbanska M**, **Gozdz A**, **Swiech LJ**, **Nagalski A**, **Perycz M**, **Blazejczyk M**, **Jaworski J**. Cyr61, a matricellular protein, is needed for dendritic arborization of hippocampal neurons. ***J Biol Chem***, 2013; 288(12):8544-59

Knapska E#, **Macias M**, Mikosz M, Nowak A, Owczarek D, Wawrzyniak M, **Pieprzyk M**, **Cymerman IA**, Werka T, Sheng M, Maren S, **Jaworski J#**, Kaczmarek L#. Functional anatomy of neural circuits regulating fear and extinction. ***Proc Natl Acad Sci***, 2012; 109(42):17093-8; # - corresponding authors

Urbanska M, **Gozdz A**, **Swiech LJ**, **Jaworski J**. Mammalian target of rapamycin complex 1 (mTORC1) and 2 (mTORC2) control the dendritic arbor morphology of hippocampal neurons. ***J Biol Chem***, 2012; 287(36):30240-56

Perycz M, **Urbanska AS**, **Krawczyk PS**, **Parobczak K**, **Jaworski J**. Zipcode binding protein 1 regulates the development of dendritic arbors in hippocampal neurons. ***J Neurosci***, 2011; 31(14):5271-85

Swiech L, **Blazejczyk M**, **Urbanska M**, **Pietruszka P**, Dortland BR, **Malik AR**, Wulf PS, Hoogenraad CC, **Jaworski J**. CLIP-170 and IQGAP1 cooperatively regulate dendrite morphology. ***J Neurosci***, 2011; 31(12):4555-68

Jaworski J, Kapitein LC, Montenegro Gouveia S, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler SA, Di Stefano P, Demmers J, Krugers H, Defilippi P, Akhmanova A, Hoogenraad CC. Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. ***Neuron***, 2009; 61:85-100

^Jaworski J, Spangler S, Seeburg DP, Hoogenraad CC, Sheng M. Control of dendritic arborization by the phosphoinositide-3'-kinase-Akt-mammalian target of rapamycin pathway. ***J Neurosci***, 2005; 25(49):11300-12

^Jaworski J, Mioduszewska B, Sanchez-Capelo A, Figiel I, Habas A, Gozdz A, Proszynki T, Hetman H, Mallet J, Kaczmarek L. Inducible cAMP early repressor, an endogenous antagonist of cAMP responsive element-binding protein, evokes neuronal apoptosis *in vitro*. ***J Neurosci***, 2003; 23(11):4519-26

^Jaworski J, Biederman IW, Lapinska J, Szklarczyk A, Figiel I, Konopka D, Nowicka D, Filipkowski RK, Hetman M, Kowalczyk A, Kaczmarek L. Neuronal excitation-driven and AP-1-dependent activation of timp1 gene expression in rodent hippocampus. ***J Biol Chem***, 1999; 274(40): 28106-12

^no IIMCB affiliation

Mammalian/mechanistic target of rapamycin (mTOR) is a serine-threonine kinase that is involved in almost every aspect of mammalian cell function. It forms two protein complexes, initially identified as regulating translation (mTORC1) or influencing the actin cytoskeleton (mTORC2). My postdoctoral work showed that the regulation of mTOR-dependent translation contributes to dendritogenesis (Jaworski et al., J Neurosci, 2005). However, the list of cellular processes that involve both mTORCs has expanded, and new ways of regulating mTORC activity, novel mTOR partners, and mTOR effectors have been discovered. Nonetheless, their contribution to the neuronal functions of mTOR and neuropathology is still poorly understood. Therefore, since the inception of our laboratory, we have sought to identify mTOR partners and regulated proteins that are involved in the neuronal development and characterization of mTOR dysfunction in neuropathology.

To achieve our scientific objectives, we have been using a well-established, relatively simple, and robust model of the dendritogenesis of neurons that are cultured in vitro. Using this approach, we previously performed both proof-of-principle experiments and unbiased screens that clearly showed that mTOR functions during neuronal development beyond the canonical control of translation (Swiech et al., J Neurosci, 2011; Urbanska et al., J Biol Chem, 2012; Malik et al., J Biol Chem, 2013; Urbanska et al., 2017). As a result, we identified several proteins that are involved in various steps of intracellular trafficking, including cytoskeleton-based transport and membrane trafficking control. Therefore, our current research focuses on an interplay between mTOR complexes and molecular motors, such as the dynein-dynactin complex and kinesins, and small GTPases of the Rab family and their regulators. Particularly interesting for us is the retromer complex, which is responsible for the retrieval of cargo from the endocytic pathway. Apart from this mainstream focus, in 2018 we continued our research on nuclear functions of mTOR in response to neuronal activity. Notably, all of these aspects are studied from two angles: basic physiology and mTOR-related disorders of the nervous system, such as tuberous sclerosis complex. For the latter, we use several state-of-the-art models, including iPSC-derived neurons, organoids, and genetically modified zebrafish.

Focusing on various aspects of the control of dendritic arbor morphology, we have realized that a large gap exists in knowledge about this phenomenon. Neurons are the most polarized cells, and their shape reflects and defines their function. Three compartments of a neuron can be distinguished: cell soma, dendrites, and axon. The primary purpose of dendrites, which often form complex structures called dendritic arbors, is to receive and compute synaptic inputs that come from other cells within a particular neuronal network. Theoretical predictions, followed by experimental work, has shown that the shape and size of dendritic arbors determine the number of inputs that are received by neurons and the efficacy of synaptic signal propagation toward the cell soma. Thus, these parameters of neuronal morphology are unique for different types of neurons and reflect their perfect adjustment to the functions they play within particular neuronal networks. Although still far from a detailed description, dendritic arbor development is quite well studied and understood. Once established, the shape of dendritic arbors remains intact through the neuron's lifespan. Given the fact that dendrites must remain intact for more than 80% of a neuron's lifetime, surprisingly little is known about the molecular mechanisms that underlie this phenomenon. To date, very few proteins have been identified to be key for the stability of mature dendritic arbors. Among those that we have identified are transcription factors, kinases, RNA binding proteins, and matricellular proteins. This variety suggests that the stabilization of dendritic arbors of mature neurons is an active process that requires sophisticated molecular machinery that is partly different from the machinery that is needed for dendritic arbor growth. Thus, we have set new objectives for our laboratory for the next few years. The first objective is to identify critical proteins and cellular processes that underlie dendritic arbor stability in the mature brain. Under physiological conditions, the shape of dendritic arbors remains stable most of the time, but this situation changes under pathological conditions. Disturbances in dendritic arbor stability in the mature brain are related to prolonged stress and mood disorders (e.g., depression). At later stages of brain aging when cognitive decline is apparent, dendrites may deteriorate. Thus, we hypothesize that a better understanding of the molecular mechanisms of dendrite stability will contribute to the development of new treatments for mood disorders and improve outcomes of brain aging. Therefore, our second objective is to identify chemicals or druggable targets that support dendrite stability under stress conditions. This new line of research will investigate the most fundamental and unexplored aspects of the brain and be performed within the framework of a TEAM grant that was awarded to our laboratory by the Foundation for Polish Science.

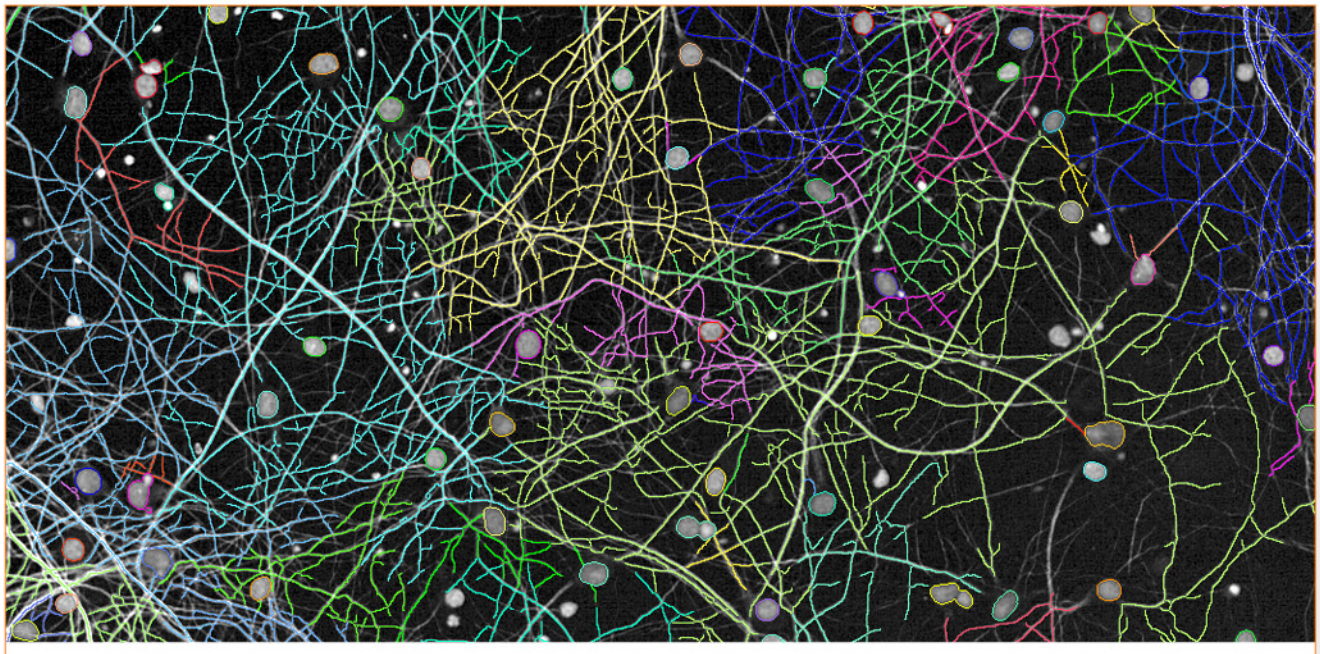

Fig. 1 Automatic tracings of dendritic networks of in vitro cultured neurons obtained with Opera Phenix system. Authors: Magdalena Mlostek, Małgorzata Urbańska

Laboratory of Neurodegeneration

GROUP MEMBERS

Lab Leader
Jacek Kuźnicki, PhD, Professor

Senior Researcher, Vice Head
Łukasz Majewski, PhD

Senior Researchers
Magdalena Czeredys, PhD
Joanna Gruszczyńska-Biegała, PhD (until September 2018)
Vladimir Korzh, PhD
Smijin Karthully Soman, PhD (until August 2018)
Tomasz Węgierski, PhD (part-time)
Małgorzata Wiweger, PhD

Postdoctoral Researchers
Evgeny Gasanov, PhD
Oksana Palchevska, PhD

Research Assistant
Michał Bazała, MSc

PhD Students
Kinga Gazda, MSc Eng. (until March 2018)
Justyna Jędrychowska, MSc
Rishikesh Kumar Gupta, M Tech.
Filip Maciąg, MSc Eng.
Iga Wasilewska, MSc

Research Technician
Sergii Palchevskyi, PhD

MSc Student
Klaudia Strucińska (until June 2018)

Trainee
Weronika Jasińska (until March 2018)

Technician
Monika Matuszczyk (part-time)

Laboratory-Administrative Partner
Dominika Dubicka-Boroch, MSc
(since December 2018)

LAB LEADER

Jacek Kuźnicki, PhD, Professor

CURRICULUM VITAE

DEGREES

1993	Professor of Biological Sciences, nomination by the President of the Republic of Poland
1987	DSc Habil in Biochemistry, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1980	PhD in Biochemistry, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1976	MSc in Biochemistry, Warsaw University, Poland

PROFESSIONAL TRAINING

July 2018	Visiting Professor, Laboratory of H. Burgess, NICHD, Bethesda, MD, USA
July 2015	Visiting Professor, Laboratory of W. Harris, University of Cambridge, UK
July 2014	Visiting Professor, Laboratory of B.E. Snaar-Jagalska, Leiden University, The Netherlands
1992-1995	Visiting Professor, Laboratory of D. Jacobowitz, Mental Health at NIH, Bethesda, MD, USA
1981-1984	Visiting Fellow (postdoc), Laboratory of E.D. Korn, NIH, Bethesda, MD, USA

PROFESSIONAL EMPLOYMENT

2017-2018	Deputy Chair of the Council of Provosts, 2nd Division, PAS
2001-2018	Director, IIMCB, Warsaw, Poland; Feb-Dec 2018 Acting Director, IIMCB, Warsaw, Poland
2001-Present	Professor, Head of Laboratory of Neurodegeneration, IIMCB, Warsaw, Poland
2000-2001	Director, Centre of Excellence Phare Sci-Tech II, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1999-2001	Acting Director, IIMCB; Organizer and Director, Centenarian Program
1996-2002	Head, Lab of Calcium Binding Proteins, professor 2002-2014 Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1991-1992	Deputy Scientific Director, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1986-1992	Associate Professor and Head, Lab of Calcium Binding Proteins, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1984-1985	Research Associate, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1980-1981	Postdoctoral Fellow, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1976-1980	PhD Student, Nencki Institute of Experimental Biology PAS, Warsaw, Poland

MEMBERSHIP IN SCIENTIFIC SOCIETIES, ORGANIZATIONS, AND PANELS

2018-2022	Member, Council of the National Science Centre, Poland
2016-Present	Member, International Advisory Board, Małopolska Centre of Biotechnology, Jagiellonian University
2011-Present	Member, International Expert Council of the Research and Education Center, State Key Laboratory of Molecular and Cellular Biology in Ukraine
2011-2014	Member, Science Policy Committee, Ministry of Science & Higher Education, Rotating President Jul-Dec 2012
2008-Present	Board Member, European Calcium Society
2008-2018	Member of the Board of Directors, Biocentrum-Ochota Consortium; Rotating President, Jul-Dec 2016, Jul-Dec 2013, Jul-Dec 2010
2006-2011	Member, Advisory Group of the 7FP for Health, European Commission
2004-Present	Corresponding Member of PAS
2004-Present	Honorary chairman, one of the founders, BioEducation Foundation
2002-Present	Head of the Program Board, Centre for Innovative Bioscience Education
1993-2014	Member, Scientific Council of the Nencki Institute of Experimental Biology PAS
1996-1998 2000-2002	Vice-President, Biotechnology Committee of PAS
1989-1991	General Secretary, Polish Biochemical Society

HONORS, PRIZES, AND AWARDS

2013	Award of the 2nd Division of Biological and Agricultural Sciences of PAS
2013	Crystal Brussels Sprout for outstanding achievements in 7FP of the European Union
2011	Konorski Award by the Polish Neuroscience Society and Committee on Neurobiology of PAS
2008	Officer's Cross of the Order of Polonia Restituta by the President of the Republic of Poland
2003	Prime Minister's Award for outstanding scientific achievements
2001	Award of the Division of Biological Sciences of PAS for work on calcium binding proteins
1998	Knight's Cross of the Order of Polonia Restituta

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Filipek A, Kordowska J, Wojda U, Hetman J, Palczewska M, Nowotny M, Billing-Marczak K, Bojarski Ł, Michowski W, Misztal K, Figiel M, Honarnejad K, Jaworska A, Gazda K.

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Wasilewska I, Gupta RK, Palchevska O, Kuznicki J. Identification of Zebrafish Calcium Toolkit Genes and their Expression in the Brain. ***Genes (Basel)***, 2019; 10(3). pii: E230

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We are interested in the molecular mechanisms that are involved in neurodegeneration, with a special emphasis on the role of Ca^{2+} homeostasis and signaling. These processes are being studied at the genomic, proteomic, and cellular levels using zebrafish, rats, and mice as model organisms. The projects are focused on proteins that are involved in store-operated Ca^{2+} entry (SOCE) and Ca^{2+} homeostasis in mitochondria, the involvement of potassium channels in the brain ventricular system, and the *in vivo* analysis of Ca^{2+} homeostasis in neurons using zebrafish models. For recent reviews, see Wegierski and Kuznicki (*Cell Calcium*, 2018) and Winata and Korzh (*FEBS Lett*, 2018).

ROLE OF STIM PROTEINS IN STORE-OPERATED CA^{2+} ENTRY IN NEURONS

We previously showed that STIM1 is involved in a thapsigargin-induced SOCE-like process, whereas STIM2 is mostly active after the EGTA-driven depletion of extracellular Ca^{2+} (Gruszczynska-Biegala et al., *PLoS One*, 2011; Gruszczynska-Biegala and Kuznicki, *J Neurochem*, 2013). We searched for new partners of STIMs other than ORAI channels and found that endogenous STIMs associate with GluA subunits of AMPA receptors (Gruszczynska-Biegala et al., *Front Cell Neurosci*, 2016). STIM proteins also associate *in vitro* with NMDA receptors. The results suggest cross-talk between STIM proteins and NMDA receptors and their effect on Ca^{2+} influx through NMDA receptors (Gruszczynska-Biegala et al., in preparation).

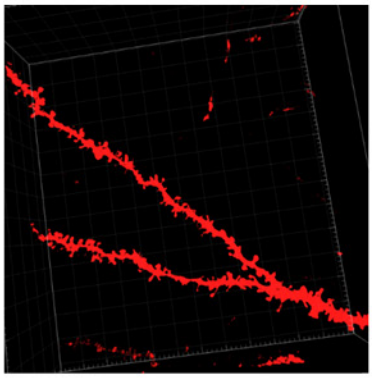
DYSREGULATION OF CA^{2+} HOMEOSTASIS IN NEURODEGENERATIVE DISEASES

The majority of animal models of Alzheimer's disease (AD) are based on the β-amyloid/tau hypothesis. However, these familial AD (FAD) models appear to have little value for understanding the mechanisms of sporadic AD (SAD; for review, see Wojda and Kuznicki, *J Alzheimers Dis*, 2013). Thus, new models need to be developed that incorporate some features of SAD. We have been testing the hypothesis that brain dysfunction during aging is induced by changes in Ca^{2+} homeostasis, which may predispose the brain to SAD pathologies. Transgenic mice that overexpressed key SOCE proteins (STIM1, STIM2, and ORAI1) specifically in brain neurons under the Thy1 promoter were generated. Characterization of the STIM1 line (Majewski et al., *BBA Mol Cell Res*, 2017) and ORAI1 lines has been reported. Strikingly, aged transgenic ORAI1 mice developed spontaneous seizure-like events that could be observed only in females, suggesting a novel, sex-dependent role of ORAI1 in neural function (Maciag, Majewski et al., BBA-MCR 2019). FAD mutations in presenilins were shown to alter both endoplasmic reticulum (ER) Ca^{2+} signaling and SOCE, but the role of amyloid precursor protein (APP) and APP FAD mutants in intracellular Ca^{2+} homeostasis is controversial. Our data indicate that APP and APP FAD mutants are not directly involved in SOCE (Wegierski et al., *Biochem Biophys Res Commun*, 2016). Instead, we found that APP knockdown resulted in the elevation of resting levels of ER Ca^{2+}, reduced Ca^{2+} leakage, and delayed the translocation of STIM1 to ORAI1 upon ER Ca^{2+} store depletion. Our data suggest a regulatory role for APP in ER Ca^{2+} (Gazda et al., *Sci Rep*, 2017). Using quantitative PCR, we compared microRNA (miRNA) profiles in blood plasma from mild cognitive impairment-AD patients (whose diagnoses were confirmed by cerebrospinal fluid [CSF] biomarkers) with AD patients and non-demented, age-matched controls. We adhered to standardized blood and CSF assays that are recommended by the JPND BIOMARKAPD consortium. Six miRNAs (three not yet reported in the context of AD and three reported in AD blood) were selected as the most promising biomarker candidates that can differentiate early AD from controls with the highest fold changes (Nagaraj et al., *Oncotarget*, 2017; patent pending: PCT/IB2016/052440).

Our studies on Huntington's disease (HD) were focused on the role of HAP1A protein in SOCE dysregulation in YAC128 mice (i.e., a model of HD). After Ca^{2+} depletion from the ER by the activation of IP_3R1, we detected an increase in the activity of SOC channels when HAP1A was overexpressed in medium spiny neurons (MSNs) from YAC128 mice. A decrease in SOC channel activity was observed when HAP1 protein was silenced. $C_{20}H_{22}BrClN_2$ was identified in our previous studies as a SOCE inhibitor and restored the elevation of SOCE in YAC128 MSN cultures. The IP_3 sponge restored the elevation of SOCE and increased the release of Ca^{2+} from the ER (Czeredys et al., *Front Cell Neurosci*, 2018). A loss-of-function mutation of *PINK1* causes early-onset Parkinson's disease in humans. In collaboration with Oliver Bandmann (University of Sheffield), we used a *pink1* mutant (*pink*$^{-/-}$) zebrafish line to study alterations of Ca^{2+} homeostasis (Flinn et al., *Ann Neurol*, 2013; Soman et al., *Eur J Neurosci*, 2016). We generated *mcu* knockout fish, which is viable and fertile. The *pink1*$^{-/-}$/*mcu*$^{-/-}$ double-knockout line shows no loss of dopaminergic neurons, suggesting that Ca^{2+} that enters mitochondria via the mitochondrial Ca^{2+} uniporter is involved in the pathology of the *pink1* mutant. We expressed a mitochondrial Ca^{2+} probe (CEPIA2mt) under a pan-neuronal promoter (*elavl3*) to visualize Ca^{2+} levels in the mitochondrial matrix of a zebrafish (we called it NeuroMitoCepia; Tg[*elavl3:CEPIA2mt*]. The probe was active in transgenic fish since 1dpf and also stable later (Fig. 1). Lightsheet fluorescence microscopy enabled us to visualize chemically inducible Ca^{2+} flux in zebrafish neurons *in vivo*. Histamine was used to increase the level of Ca^{2+} in mitochondria. Mutations of NPC2, SGSH, PPP3CA, and PTPN4 have been linked to neurological problems. Using CRISPR/Cas9 technology, we created zebrafish lines with genetic changes that mimic those that are found in patients. These fish lines are being used to study Ca^{2+} homeostasis and its impact on the progression of neurodegeneration and sleep disturbances [i.e., phenotypes that are observed in patients with Niemann-Pick C (mutation of *NPC2*), mucopolysaccharidosis type III A (*SGSH*), and calcineurin (*PPP3CA*); Rydzanicz *et al.*, 2018]). *ptpn4a* and *ptpn4b* crispants are being used to reveal the ways in which tyrosine-protein phosphatase non-receptor type 4 controls neurodevelopment and the sleep-wake cycle.

DEVELOPMENT OF HOLLOW ORGANS

Subunits of the voltage-gated potassium channels Kcnb1 (Kv2.1) and Kcng4 (Kv6.4) are expressed in several hollow organs (e.g., brain ventricular system [BVS], ear, and eye) where they form tetrameric K^+ channels and antagonize each other's activity. The deficiency of Kcnb1 in zebrafish causes microcephaly, and the gain-of-function of Kcnb1 causes hydrocephalus. Kcng4 acts in a reverse manner (Shen et al., *Sci Rep*, 2016). Formation of the BVS occurs during the early neural development of vertebrates (Korzh, *Cell Mol Life Sci*, 2018). Deficiency of the BVS has been linked to numerous neurodegenerative diseases. Formation of the BVS depends on many factors, including the ependyma (i.e., cells that line the BVS cavity and circumventricular organs, including the choroid plexus; Garcia-Lecea et al., *Front Neuroanat*, 2017). To study the role of K^+ channels in the development of hollow organs, we are currently designing and developing transgenic knockin zebrafish that express fluorescent proteins in cells that line the BVS and ear under the control of Kcng4b regulatory elements and mutants of Kcng4b using the CRISPR-Cas9 mutagenesis system.



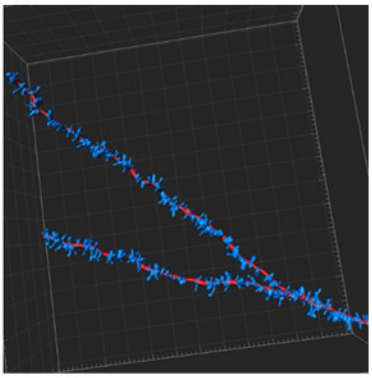


Fig. 1 DiI labeling of hippocampal neuron from *Tg(Orai1)Ibd mice (red) and dendriticspine reconstruction by IMARIS software*(blue). Author: Łukasz Majewski

Laboratory of Cell Biology

GROUP MEMBERS

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Małgorzata Maksymowicz, MSc
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Kamila Kozik, Eng.
Michał Mazur, Eng. (until September 2018)
Karolina Romaniuk, Eng. (since May 2018)
Patryk Ślusarczyk, Eng. (until May 2018)
Małgorzata Świątek, Eng.

Trainees
Michał Mazur, Msc (since October 2018)
Paulina Nowak, MSc (until August 2018)
Blair Stewig, BSc (Fulbright Student Researcher, since October 2018)
Renata Wyszyńska, MSc (until September 2018)

Technician
Monika Matuszczyk (part-time)

Laboratory-Administrative Partner
Paulina Okafor, MSc (until September 2018)
Renata Wyszyńska, MSc (since October 2018)

LAB LEADER

Marta Miączyńska, PhD, Professor

CURRICULUM VITAE

DEGREES

2013	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2008	DSc Habil in Cell Biology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1997	PhD in Genetics, University of Vienna, Austria
1993	MSc in Molecular Biology, Jagiellonian University, Cracow, Poland
1991	BSc in Biological Sciences, University of Wolverhampton, UK

PROFESSIONAL EMPLOYMENT

2018-Present	Director, IIMCB, Warsaw, Poland
June 2014 -Dec 2015	Deputy Director for Scientific Matters, IIMCB, Warsaw, Poland
June 2013 -May 2014	Deputy Director, IIMCB, Warsaw, Poland
2005-Present	Professor, Head of Laboratory of Cell Biology, IIMCB, Warsaw, Poland

RESEARCH TRAINING

2001-2005	Senior Postdoctoral Fellow, Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG), Dresden, Germany
1997-2002	Postdoctoral training, European Molecular Biology Laboratory, Heidelberg, Germany
1993-1996	PhD studies, Institute of Microbiology and Genetics, University of Vienna, Austria
1990-1991	Exchange Student, University of Wolverhampton, UK

HONORS, PRIZES, AND AWARDS

2017	EMBO Member
2016-2018	Member, Council of the National Science Centre
2016	TEAM, Foundation for Polish Science
2012	MAESTRO, National Science Centre
2011	Polish-Swiss Research Programme
2007	Habilitation Fellowship of L'Oreal Poland for Women in Science
2006-2012	International Senior Research Fellowship, Wellcome Trust, UK
2006-2010	International Research Scholar, Howard Hughes Medical Institute, USA
2006-2010	Partner Group grant, Max Planck Society, Germany
2001-2004	Postdoctoral Fellowship, Max Planck Society, Germany
1999-2000	Long-Term Postdoctoral Fellowship, Human Frontier Science Program Organization (HFSPO)
1998-1999	Erwin Schrödinger Postdoctoral Fellowship, Austrian Science Fund
1993-1996	Bertha von Suttner PhD Scholarship, Austrian Ministry of Science
1990-1991	Studentship, European Community Tempus Scheme

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Olchowik M, Urbańska A, Hupałowska A, Sadowski Ł, Mamińska A, Toruń A, Jastrzębski K.

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Banach-Orłowska M, Jastrzębski K, Cendrowski J, Maksymowicz M, Wojciechowska K, Korostyński M, Moreau D, Gruenberg J, **Miaczynska M.** The topology of lymphotoxin β receptor accumulated upon endolysosomal dysfunction dictates the NF-κB signaling outcome. ***J Cell Sci,*** 2018; 131(22) pii: jcs218883

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Sadowski L, Pilecka I, Miaczynska M. Signaling from endosomes: Location makes a difference. (Review) ***Exp Cell Res***, 2009; 315:1601-09

Ohya T, **^Miaczynska M,** Coskun U, Lommer B, Runge A, Drechsel D, Kalaidzidis Y, Zerial M. Reconstitution of Rab- and SNAREdependent membrane fusion by synthetic endosomes. ***Nature***, 2009; 459:1091-97

Miaczynska M, Stenmark H. Mechanisms and functions of endocytosis. ***J Cell Biol***, 2008; 80:7-11

Pilecka I, Banach-Orlowska M, Miaczynska M. Nuclear functions of endocytic proteins. ***Eur J Cell Biol***, 2007; 86:533-547

^Miaczynska M, Pelkmans L, Zerial M. Not just a sink: endosomes in control of signal transduction. (Review) ***Curr Opin Cell Biol***, 2004; 16:400-406

^Miaczynska M, Christoforidis S, Giner A, Shevchenko A, Uttenweiler-Joseph S, Habermann B, Wilm M, Parton RG, Zerial M. APPL proteins link Rab5 to signal transduction via an endosomal compartment. ***Cell***, 2004; 116:445-56

^ no IIMCB affiliation

We study the ways in which intracellular signal transduction and membrane trafficking in endocytosis are integrated at the molecular level. We focus on proteins that play well-known roles in endocytosis to investigate their involvement in various signaling pathways and their impact on patterns of gene expression. Initially, our efforts were focused on studying the endosomal and nuclear roles of APPL proteins. In recent years, we broadened our interests to other multifunctional proteins that act in endocytosis and signaling. The specific projects that are developed by our group seek to answer the following questions:

- What is the role of endosomal compartments in the trafficking and signaling of growth factors and cytokines?
- How does the endocytic trafficking of receptors impinge on the patterns of gene expression in different signaling pathways?
- What are the consequences of endosomal dysfunction in the cell?

Endocytosis was first viewed simply as a mechanism of signal termination through the downregulation and degradation of surface receptors. However, more recent data indicate that endosomal compartments and their resident proteins play an important role in transmitting intracellular signals by transporting ligand-receptor complexes and affecting their activity inside the cell (Cendrowski et al., *Cytokine Growth Factor Rev*, 2016; Hupalowska and Miaczynska, *Traffic*, 2012; Miaczynska, *Cold Spring Harb Perspect Biol*, 2013; Miaczynska and Bar-Sagi, *Curr Opin Cell Biol*, 2010; Sadowski et al., *Exp Cell Res*, 2009; Szymanska et al., *Semin Cell Dev Biol*, 2018). Moreover, several endocytic proteins can undergo nucleocytoplasmic shuttling and interact with nuclear molecules that are involved in transcription or chromatin remodeling, changing their localization or activity, and thus may directly modulate the levels or specificity of gene transcription (Pilecka et al., *Eur J Cell Biol*, 2007). Importantly, some such dual-function endocytic and nuclear proteins affect cell proliferation or act as tumor suppressors, or their expression changes in human cancers (Pyrzyńska et al., *Mol Oncol*, 2009).

In one of our previous projects, we identified four components of endosomal sorting complexes required for transport (ESCRTs) as novel inhibitors of NF-κB signaling (Mamińska et al., *Sci Signal*, 2016). We found that the depletion of Tsg101, Vps28, UBAP1, and CHMP4B in the absence of cytokine stimulation potently activated both canonical and noncanonical NF-κB signaling. This led to upregulation of the expression of NF-κB target genes in cultured human cells, zebrafish embryos, and fat bodies in flies. These effects depended on cytokine receptors, such as lymphotoxin β receptor (LTβR) and tumor necrosis factor receptor 1 (TNFR1). Upon the depletion of ESCRT subunits, both receptors became concentrated on and signaled from endosomes. The endosomal accumulation of LTβR induced its ligand-independent oligomerization and inflammatory NF-κB signaling. As a conclusion of this study, we proposed that ESCRTs constitutively control the distribution of cytokine receptors in their ligand-free state to restrict their signaling.

As a follow-up of this work, we further investigated the mechanisms of intracellular trafficking and inflammatory signaling by LTβR. In particular, we studied whether other perturbations of endosomal transport, in addition to the depletion of ESCRT subunits, trigger LTβR activation and signaling. We focused on two related endosomal sorting complexes: class C core vacuole/endosome tethering (CORVET) and homotypic fusion and protein sorting (HOPS). By knocking down the individual components of both complexes, we found out that the HOPS complex but not the CORVET complex mediates the endocytic trafficking of LTβR. The depletion of HOPS subunits led to the accumulation of ligand-free LTβR on endosomal compartments and an increase in its interactions with TRAF2/TRAF3 signaling adaptors. Similar effects were observed upon the knockdown of Rab7, a small GTPase that regulates endosome maturation toward lysosomes, and upon the pharmacological inhibition of lysosomal degradation. Surprisingly, however, LTβR that accumulated on endosomes under these conditions did not induce the NF-κB pathway, in contrast to the active signaling of LTβR from endosomes that occurred upon ESCRT dysfunction. We explained this apparent discrepancy by performing an in-depth analysis of LTβR localization within endosomes. LTβR was present in internal, so-called intraluminal, vesicles of endosomes when HOPS subunits or Rab7 were depleted. This sequestration of LTβR inside endosomes prevented active signaling because the receptor was segregated away from the cytoplasm that contains the necessary signaling components of the NF-κB pathway. In turn, the depletion of ESCRT components is known to perturb the formation of intraluminal vesicles of endosomes. Therefore, under these conditions, LTβR was localized to the outer endosomal membrane and exposed to the cytoplasm that was permissive for NF-κB signaling. We generally concluded that various types of endolysosomal dysfunction lead to the accumulation of LTβR on endosomes, but the exact topology of the receptor within these compartments determines whether NF-κB signaling is induced or prevented (Banach-Orłowska et al., *J Cell Sci*, 2018).

Finally, in an ongoing TEAM grant from the Foundation for Polish Science, we are studying the consequences of impairments in endosomal function on cellular protein homeostasis and metabolism. In collaboration with scientists from the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, we are also investigating the function of endosomes in cancer cells and the possibility of its pharmacological modulation.

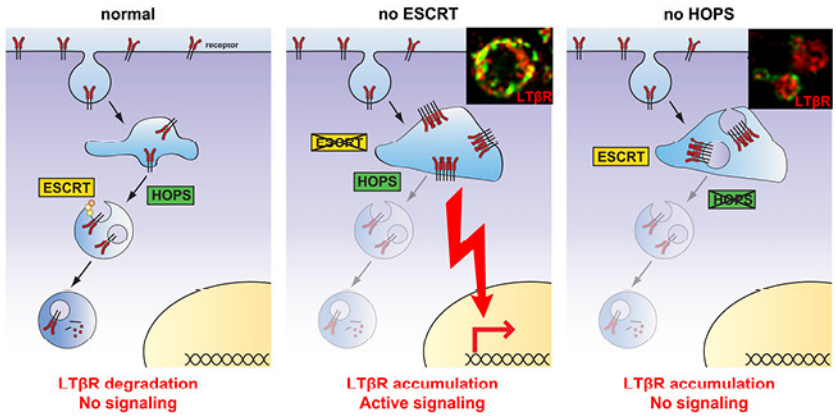

Fig. 1 Model of different LTβR topologies and signaling upon the dysfunction of various trafficking regulators. Under normal conditions (left), ligand-free LTβR is degraded in lysosomes and does not induce signaling. Upon the depletion of ESCRT components (middle), LTβR accumulates on the outer membrane of endosomes, and this local accumulation leads to its oligomerization and activation, inducing inflammatory NF-κB signaling. Upon the depletion of HOPS subunits (right), LTβR accumulates in internal vesicles inside endosomes that isolate the receptor from the cytoplasm and prevent its signaling. Insets in the middle and right diagrams show microscopy images of endosomes, visualized by EEA1 staining (green) and containing LTβR (red) under conditions of ESCRT or HOPS depletion.

Authors: Kamil Jastrzębski, Marta Miączyńska

Laboratory of Iron Homeostasis

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Gabriela Jędruszewska, MSc
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Marta Niklewicz (part-time)

Laboratory-Administrative Partner
Aleksandra Szybińska, MSc (part-time)

LAB LEADER

Katarzyna Mleczko-Sanecka, PhD

CURRICULUM VITAE

DEGREES

2011	PhD in Biology, European Molecular Biology Laboratory (EMBL) Heidelberg and Heidelberg University, Germany
2007	MSc in Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Cracow, Poland

RESEARCH EXPERIENCE

2017-Present	Professor, Head of Laboratory of Iron Homeostasis, IIMCB, Warsaw, Poland
2011-2015	Post-doctoral research with Prof. Martina Muckenthaler and Prof. Matthias W. Hentze, Molecular Medicine Partnership Unit, EMBL Heidelberg and Heidelberg University, Germany
2007-2011	Doctoral research with Prof. Martina Muckenthaler and Prof. Matthias W. Hentze, Molecular Medicine Partnership Unit, EMBL Heidelberg and Heidelberg University, Germany
2006-2007	Master thesis research in the laboratory of Prof. Józef Dulak and Prof. Alicja Józkowicz, Department of Medical Biotechnology, Jagiellonian University, Cracow, Poland
2006	Undergraduate research during Erasmus fellowship at the Centre De Biophysique Moleculaire in Dr. Claudine Kieda's laboratory, CNRS, Orleans, France
2005	Undergraduate research Erasmus Scholarship at the Centre De Biophysique Moleculaire in Dr. Claudine Kieda's laboratory, CNRS, Orleans, France

HONORS, PRIZES, AND AWARDS

2016	Polonez, National Science Centre
2014	Independent research grant from the University of Heidelberg
2011	Invitation for the 61st Lindau Meeting of Nobel Laureates, Lindau, Germany
2015, 2014, 2011, 2010, 2009	Travel Grants to attend and present data at the international conferences in iron biology
2007	The Louis-Jeantet PhD Scholarship for young researchers from Eastern Europe supporting PhD studies at EMBL
2006	Erasmus Scholarship at the CNRS, Orleans, France

SELECTED PUBLICATIONS

Pasricha SR, Lim PJ, Duarte TL, Casu C, Oosterhuis D, **Mleczko-Sanecka K**, Suciu M, Da Silva AR, Al-Hourani K, Arezes J, McHugh K, Gooding S, Frost JN, Wray K, Santos A, Porto G, Repapi E, Gray N, Draper SJ, Ashley N, Soilleux E, Olinga P, Muckenthaler MU, Hughes JR, Rivella S, Milne TA, Armitage AE, Drakesmith H. Hepcidin is regulated by promoter-associated histone acetylation and HDAC3. ***Nat Commun***, 2017; 8(1):403

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Funovics P, Brostjan C, Nigisch A, Fila A, Grochot A, **^Mleczko K**, Was H, Weigel G, Dulak J, Jozkowicz A. Effects of 15d-PGJ(2) on VEGF-induced angiogenic activities and expression of VEGF receptors in endothelial cells.***Prostaglandins Other Lipid Mediat***, 2006; 79(3-4):230-244

^ no IIMCB affiliation

DESCRIPTION OF CURRENT RESEARCH

Sufficient iron supplies are critical for vital cellular functions, such as energy production and RNA/DNA processing and repair. In the human body, the vast majority of iron is utilized for hemoglobin synthesis during the daily production of ~200 billion erythrocytes. However, an excess of free iron can cause oxidative damage and lead to organ failure. The maintenance of iron balance is thus essential for the proper functioning of cells and organisms. Broadening our knowledge of the genetic control of iron homeostasis is important for human health. The major objective of research in the Laboratory of Iron Homeostasis is to better understand the processes that impact systemic and cellular iron levels and identify new players in iron-regulatory pathways.

At the systemic level, more than 90% of daily iron needs are met by internal iron recycling from senescent erythrocytes by splenic macrophages. The iron pool in the body is largely preserved. Because iron excretion is unregulated, iron acquisition in the intestine and its release from splenic macrophage stores must be tightly controlled. These tasks are chiefly fulfilled by the master iron-regulatory hormone hepcidin. When iron levels in the body increase, hepcidin production is enhanced to prevent further iron absorption from the diet. To gain insights into the genetic control of iron homeostasis, we previously designed and conducted large-scale RNAi screens for novel hepcidin regulators. Follow-up work of our unbiased screens (i) revealed that SMAD7 is an important hepcidin inhibitor, (ii) linked hepcidin control to proliferative signaling, and (iii) aided in the identification of two commonly prescribed drugs, the antihypertensive drug spironolactone and antineoplastic drug imatinib, as hepcidin-suppressing agents in cultured cells and mice (Mleczko-Sanecka et al., 2010, 2014, 2017). Nevertheless, despite growing knowledge of the molecular control of iron homeostasis, the genetic basis for variations in body iron parameters is still not fully understood. Thus, identifying elusive factors that modify such processes as iron sensing, iron flux, and iron accumulation has high medical relevance.

When iron levels in the body increase, iron-sensing mechanisms are engaged to enhance hepcidin production and prevent further dietary iron uptake. BMP signaling is a key pathway for iron-dependent hepcidin regulation. Among a few BMP cytokines that were shown to stimulate hepcidin transcription in vitro, BMP6 emerged as a critical endogenous factor that maintains systemic iron homeostasis (Fig. 1). The transcription of Bmp6 is oppositely regulated in mice by iron-rich and iron-deficient diets, and this phenomenon occurs specifically in the liver. Bmp6 knockout mice exhibit marked hepcidin deficiency and develop severe iron overload. Recent studies identified endothelial liver sinusoidal endothelial cells (LSECs) as major producers of liver BMP6 and found that mice with endothelial-specific Bmp6 deletion recapitulate phenotypes of the systemic Bmp6 knockout model. Altogether, these data indicate that BMP6 functions as a key angiocrine factor that senses body iron levels, controls hepatocytic hepcidin production, and maintains appropriate iron balance in the body. Despite this knowledge, however, still unclear are the ways in which systemic or liver iron status translates into alterations of endothelial Bmp6 mRNA levels and the ways in which different cell types in the liver may contribute to this regulation. One of our aims is to decipher these signaling events that possibly involve cell-to-cell communication in the liver and may contribute to the control of Bmp6 transcription in LSECs. Our work thus utilizes cell lines, primary liver cell cultures, and mice to increase our understanding of the exact roles of individual cell types in iron sensing.

If iron challenge persists or when hepcidin responses are dysregulated, iron levels increase. This ultimately leads to the excessive saturation of transferrin and the generation of non-transferrin bound iron (NTBI). This form of "free iron" is highly toxic and currently considered a main contributor to the pathology of iron-overload disorders. Liver hepatocytes are the primary cell type that acquires NTBI, which ultimately may lead to impairments in liver function and a higher risk of aggressive hepatocellular carcinoma. Hepatic iron accumulation is a hallmark of hereditary hemochromatosis and some severe anemias (e.g., thalassemias) and accompanies several other common liver diseases. Interestingly, the severity of iron loading, particularly in hemochromatosis, differs substantially between patients, and the genetic basis of this variation is still not fully

understood. One of our ongoing projects seeks to understand the molecular processes that contribute to NTBI iron uptake in hepatocytes. Specifically, we aim to identify signaling mechanisms that control or alter hepatic expression levels of ZIP14 (encoded by SLC39A14), the key metal transporter that is responsible for NTBI uptake in the liver (Fig. 1). ZIP14 is considered an attractive therapeutic target to prevent or limit liver iron loading. The identification of druggable ZIP14 regulators may thus reveal new pharmacological interventions and may shed light on underdiagnosed iron-related side effects of some pharmaceuticals, which we demonstrated recently for hepcidin. Insights into regulatory mechanisms of ZIP14 may also help identify genes that modify the severity of iron overload and can serve as diagnostic markers to predict which patients are at risk of developing overt clinical symptoms. The ablation of ZIP14 in zebrafish and mice and its mutation in humans were recently reported to lead to hepatic manganese (Mn) deficiency and Mn accumulation in other organs, critically in the brain where Mn deposition causes neurotoxicity. Thus, comprehensive characterization of the ZIP14 regulatory network has as well medical relevance for understanding Mn homeostasis (Fig. 1).

To decipher the ZIP14 regulome, we will apply state-of-the-art CRISPR-based genetic screens, followed by functional characterization of the most interesting hits in cellular assays and mice. We have already employed CRISPR-based gene editing techniques to generate reporter cells that are engineered to monitor endogenous levels of ZIP14 using a fluorescence-based readout (Fig. 2). We have validated such a "new-generation" reporter system by showing that CRISPR-based depletion of the newly identified ZIP14 regulator, HNF4α, as well as ZIP14 itself, efficiently reduces the fluorescent signal, which reflects responses of endogenous ZIP14 mRNA.

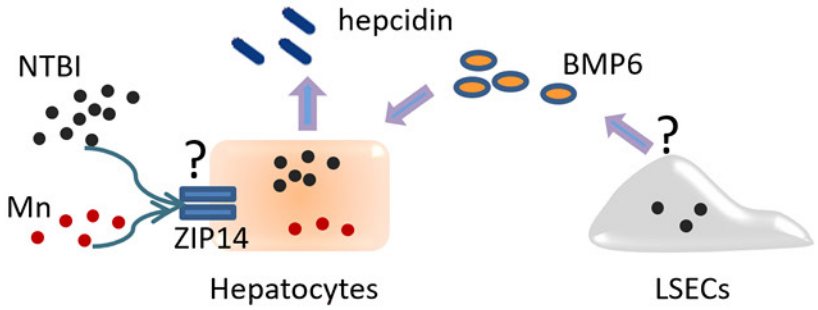

Fig. 1 Systemic iron homeostasis is maintained by the iron-regulatory hormone hepcidin. Under iron-rich conditions, hepcidin production is stimulated in hepatocytes by BMP6, an angiokine that is released from liver sinusoidal endothelial cells (LSECs). One aim of our research is to dissect the mechanisms that control the iron-triggered induction of BMP6 and to better understand the process of iron-sensing in the liver. Another major objective of work in our laboratory is to identify the mechanisms that control the expression of ZIP14, an abundant hepatocytic transporter that is responsible for the liver accumulation of non-transferrin bound iron (NTBI).

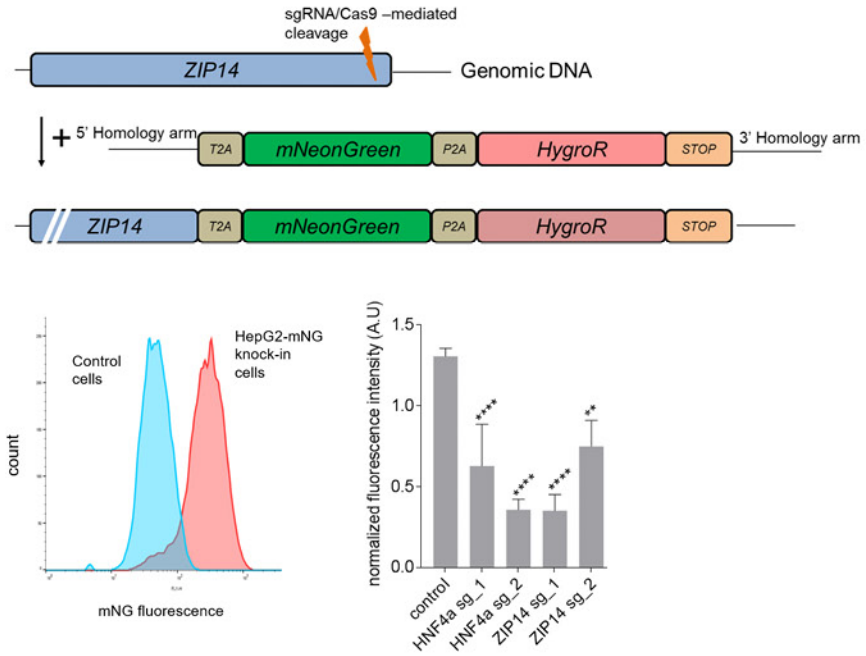

Fig. 2 Generation and validation of fluorescent ZIP14 reporter HepG2 cells. The figure shows the ZIP14 locus with CRISPR-mediated knockin of the fluorescent mNeonGreen (mNG) gene together with the hygromycin resistance gene. The fluorescence signal intensity from the engineered cells decreases upon CRIPSR knockout of the ZIP14 regulator HNF4α and ZIP14 itself.

Laboratory of Protein Structure

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Małgorzata Figiel, PhD
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Zbigniew Pietras, PhD
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Justyna Studnicka, MSc
Weronika Zajko, MSc

Technician
Iwona Ptasiewicz (part-time)

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Kinga Adamska, MSc
Agnieszka Konkol, MSc (since December 2018)

LAB LEADER

Marcin Nowotny, DSc Habil

CURRICULUM VITAE

DEGREES

2013	DSc Habil in Molecular Biology, Institute of Biochemistry and Biophysics, Warsaw, Poland
2002	PhD magna cum laude in Biochemistry, under the supervision of Prof. Jacek Kuźnicki, Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1998	MSc in Organic Chemistry and Biochemistry, Department of Chemistry, Warsaw University, Poland

PROFESSIONAL EMPLOYMENT

2015-2018	Deputy Director for Science, IIMCB, Warsaw, Poland
2008-Present	Professor, Head of the Laboratory of Protein Structure, IIMCB, Warsaw, Poland

POSTDOCTORAL TRAINING

2003-2008	Postdoctoral Fellow, Wei Yang Laboratory, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

HONORS, PRIZES, AND AWARDS

2018	Member, Scientific Policy Committee, Ministry of Science and Higher Education, Poland
2018	MAESTRO, National Science Centre
2016	TEAM, Foundation for Polish Science
2015	Jan Karol Parnas Award for the best Polish biochemical publication (with the group of Prof. Janusz M. Bujnicki)
2015	STRATEGMED, National Centre for Research and Development, Poland
2013	Academia Europea Burgen Scholar
2013	Knight's Cross of the Order of Polonia Restituta
2012	Polish Prime Minister's Award for scientific achievement
2012	„Ideas for Poland" Award, Foundation for Polish Science
2012	Jan Karol Parnas Award for the best Polish biochemical publication
2012	Wellcome Trust Senior Research Fellowship (renewal)
2012	HHMI Early Career Scientist Award
2011	ERC Starting Grant
2007	EMBO Installation Grant
2007	Wellcome Trust Senior Research Fellowship
2003	Prime Minister's Award for PhD thesis
2001, 2002	Annual Stipend for Young Scientists, Foundation for Polish Science

DOCTORATES DEFENDED UNDER LAB LEADER'S SUPERVISION

Jaciuk M, Miętus M, Czarnocki-Cieciura M, Śmietański M.

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Razew M, Warkocki Z, Taube M, Kolondra A, **Czarnocki-Cieciura M**, **Nowak E**, Labedzka-Dmoch K, Kawinska A, Piatkowski J, Golik P, Kozak M, Dziembowski A, **Nowotny M**. Structural analysis of mtEXO mitochondrial RNA degradosome reveals tight coupling of nuclease and helicase components. ***Nat Commun***, 2018; 9(1):97

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Gaur V, Wyatt HDM, **Komorowska W**, Szczepanowski RH, de Sanctis D, **Gorecka KM**, West SC, **Nowotny M**. Structural and Mechanistic Analysis of the Slx1-Slx4 Endonuclease. ***Cell Rep***, 2015, 10(9):1467-76

Miętus M, **Nowak E**, **Jaciuk M**, **Kustosz P**, **Studnicka J**, **Nowotny M**. Crystal structure of the catalytic core of Rad2: insights into the mechanism of substrate binding. ***Nucleic Acids Res***, 2014; 42(16):10762-75

Figiel M, **Nowotny M**. Crystal structure of RNase H3-substrate complex reveals parallel evolution of RNA/DNA hybrid recognition. ***Nucleic Acids Res***, 2014; 42(14):9285-94

Nowak E, Miller JT, Bona MK, **Studnicka J, Szczepanowski RH, Jurkowski J**, Le Grice SFJ[§], **Nowotny M**[§]. Ty3 reverse transcriptase complexed with an RNA-DNA hybrid shows structural and functional asymmetry. ***Nat Struct Mol Biol,*** 2014; 21(4):389-396; [§]corresponding authors

Smietanski M*, Werner M*, Purta E, Kaminska KH, Stepinski J, Darzynkiewicz E, **Nowotny M**[§], Bujnicki JM§. Structural analysis of human 2'-O-ribose methyltransferases involved in mRNA cap structure formation. ***Nat Commun,*** 2014; 5:3004; §corresponding authors, *equally contributing

Górecka KM, Komorowska W, Nowotny M. Crystal structure of RuvC resolvase in complex with Holliday junction substrate. ***Nucleic Acids Res,*** 2013; 41(21):9945-55

Nowak E, Potrzebowski W, Konarev P, Rausch J, Bona M, Svergun DI, Bujnicki JM, Le Grice SF, **Nowotny M**. Structural analysis of monomeric retroviral reverse transcriptase in complex with an RNA/DNA hybrid. ***Nucleic Acids Res,*** 2013; 41(6):3874-87

Figiel M, Chon H, Cerritelli SM, **Cybulska M**, Crouch RJ, **Nowotny M**. The structural and biochemical characterization of human RNase H2 complex reveals the molecular basis for substrate recognition and Aicardi-Goutieres syndrome defects. ***J Biol Chem,*** 2011; 286(12):10540-50

Jaciuk M, Nowak E, Skowronek K, **Tanska A, Nowotny M**. Structure of UvrA nucleotide excision repair protein in complex with modified DNA. ***Nat Struct Mol Biol,*** 2011; 18(2):191-197

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Nowotny M, Yang W. Structural and functional modules in RNA interference (review). ***Curr Opin Struct Biol,*** 2009; 19(3):286-293

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^Nowotny M, Gaidamakov SA, Ghirlando R, Cerritelli SM, Crouch RJ, Yang W. Structure of human RNase H1 complexed with an RNA/DNA hybrid: insight into HIV reverse transcription. ***Mol Cell,*** 2007; 28(2):264-276

^Nowotny M, Gaidamakov SA, Crouch RJ, Yang W. Crystal structures of RNase H bound to an RNA/DNA hybrid: substrate specificity and metal-dependent catalysis. ***Cell,*** 2005; 121(7):1005-16

^ no IIMCB affiliation

DESCRIPTION OF CURRENT RESEARCH

Our laboratory focuses on structural and biochemical studies of nucleic acid enzymes using protein crystallography as a primary method. The key results that have been obtained recently by our group concern RNA turnover and reverse transcriptases (RTs).

Mechanism of mitochondrial RNA degradation

RNA metabolism, the regulation of gene expression, and the efficient removal of defective RNA molecules critically rely on RNA degradation pathways. This degradation is mainly achieved by the action of processive exoribonucleases that can act from either end of RNA molecules. They often form assemblies with other proteins to enhance their effectiveness. For example, exoribonucleases that exhibit 3'-to-5' directionality can work together with RNA helicases that are believed to facilitate substrate recruitment and help unwind structured RNAs. One example of such cooperation is the yeast mitochondrial RNA degradosome (mtEXO) complex. It is composed of two subunits: the metal-dependent 3'-to-5' exoribonuclease Dss1 and the nucleotide triphosphate (NTP)-dependent RNA helicase Suv3 that has the same directionality. Both proteins are encoded by nuclear genes. Mutations of either gene cause the accumulation of excision introns and RNA precursors, thus lowering the level of mature transcripts and consequently leading to loss of the mitochondrial genome. The mtEXO complex can be reconstituted *in vitro* with a 1:1 Dss1:Suv3 stoichiometry. Biochemical studies revealed that both subunits share a remarkable functional interdependence of their nuclease and helicase activity within the complex.

The aim of our research was to understand the mechanism of action of mtEXO and particularly the basis of the tight interdependence of the helicase and nuclease activities. We solved a crystal structure of Dss1 exoribonuclease from *Candida glabrata* (PDB ID: 6F3H), which showed that the enzyme is a unique member of the RNase II-like family with special N-terminal domains—β-barrel, winged-helix,

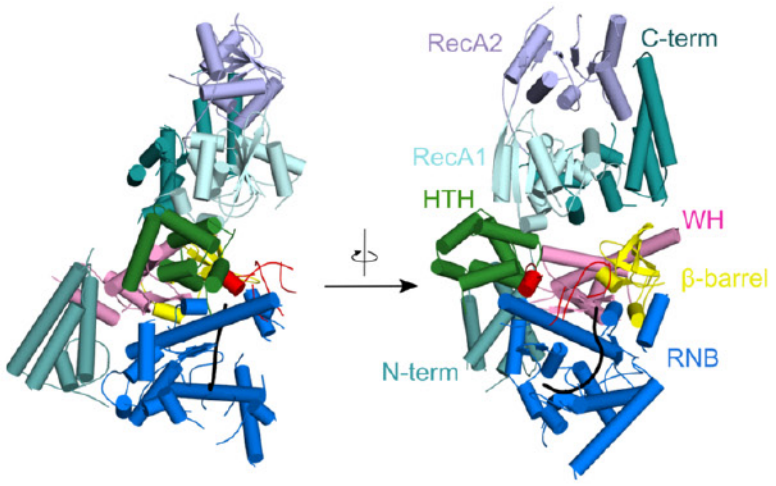

Fig. 1 The crystallographic structure of the mtEXO complex from Candida glabrata (PDB ID: 6F4A). Within the complex, the entry to the RNA-binding channel of Dss1 is occupied by the Suv3 helicase ring that interacts with the unique domains decorating the RNB catalytic domain of Dss1 (marked in blue). The co-crystallized RNA that is trapped inside the RNB domain is shown in black.

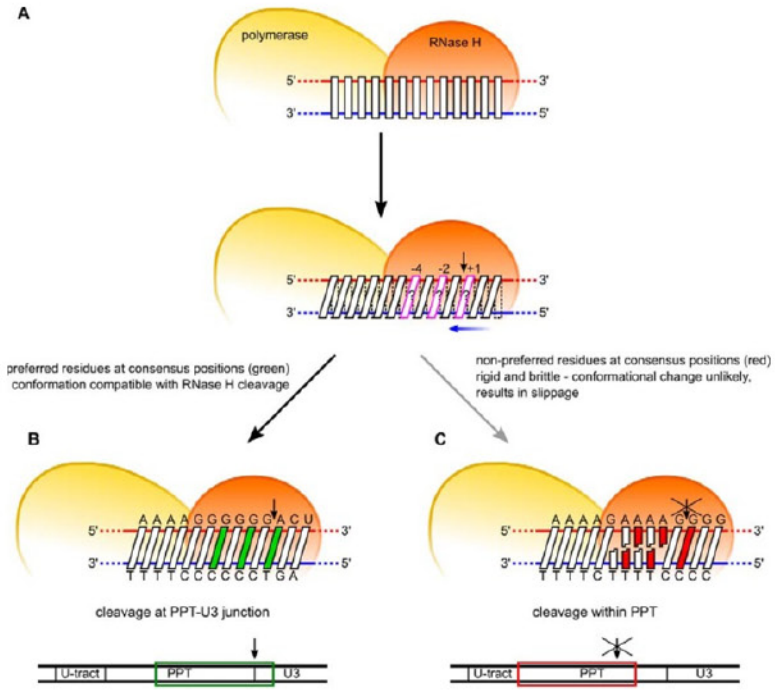

Fig. 2 Model of PPT recognition by HIV-1 RT. Comparison of interactions of RNase H domain with a preferred (PPT-U3 junction) and non-preferred (PPT) substrate. Preferred and non-preferred residues at the consensus positions of the substrate are shown in green and red, respectively. Deformation of the poly-A sequence of the substrate is represented by broken boxes.

and helix-turn-helix—that replaced the typically observed Cold Shock Domains. We also determined a crystallographic structure of the mtEXO complex from *Candida glabrata* (PDB ID: 6F4A), which for the first time showed the spatial orientation of both of its subunits within a functional complex. The arrangement of the two proteins enables the helicase motor to feed the free 3' end of the RNA molecule toward the exoribonuclease active site where efficient digestion of the substrate occurs. The protein-protein interface is formed between the RecA1 domain of Suv3 helicase and the two specialized domains of Dss1: winged-helix and helix-turn-helix. This allows the complex to accommodate conformational changes in the Suv3 ATPase cycle.

The cooperation of both activities is particularly important in the context of the degradation of structured RNA molecules that Dss1 nuclease is unable to digest. Only the unwinding of their secondary structure by the Suv3 helicase and the release of the free 3' end toward the Dss1 catalytic channel enables further degradation. This work was performed in collaboration with Prof. Andrzej Dziembowski and Prof. Paweł Golik (Razew et al., *Nat Commun*, 2018).

Reverse transcriptases

Reverse transcriptases catalyze the process of the conversion of single-stranded RNA to double-stranded DNA. This reaction is termed reverse transcription and a critical step in the proliferation of retroviruses, such as human immunodeficiency virus (HIV) and the most successful genetic mobile elements (i.e., retroelements). Two activities of RTs are required for reverse transcription: DNA polymerase synthesizes the new DNA, and RNase H degrades the RNA/DNA intermediate of the reaction. HIV RT is a heterodimer, and its larger subunit harbors both polymerase and RNase H activities. Our aim was to elucidate the mechanism of coordination of these two enzymatic activities of HIV-1 RT (Figiel et al., *Nucleic Acids Res*, 2017). A number of structures are available for the enzyme in complex with various nucleic acid substrates. In some of the structures, the substrate interacted with the polymerase active site, but none of them captured the catalytic interaction between the substrate and the RNase H domain. To characterize the conformation that corresponds to this catalytic interaction, we used an approach that combines chemical cross-linking between the protein and nucleic acid using molecular dynamics simulations. We found that the interaction between the substrate and RNase H domain involves conformational changes in both the protein and the nucleic acid (i.e., untwisting of the double helix and narrowing of the minor groove). Importantly and contrary to the results of structural studies, when the substrate interacts with the RNase H active site, it can also be productively engaged at the polymerase active site. Such a configuration has not yet been captured in crystal structures and thus corresponds to a potential transient state of the protein-substrate complex. This demonstrates the existence of transient conformations that are essential for the mechanism of nucleic acid enzymes. This work was performed in collaboration with Prof. Jarosław Poznański (IBB, Polish Academy of Sciences).

A critical yet poorly understood step of the reverse transcription reaction is the generation of the polypurine tract (PPT) primer for the synthesis of (+)-strand DNA. The PPT comprises 15 ribonucleotides, including a stretch of eight adenines with a single intervening guanine, followed by a stretch of six guanines. The PPT primer is generated by protecting its body from cleavage by RNase H and the introduction of specific cuts at the PPT termini. We prepared covalently tethered HIV-1 RT–PPT nucleic acid complexes. We found that recognition of the PPT occurred within these covalent complexes, indicating that the PPT is generated in the catalytic complex after its formation. We showed that two elements are involved in PPT recognition, and both rely on the specific sequence of the PPT. The first is RNase H sequence preference. The second is the inability of the poly-rA/dT tract of the PPT to adopt a conformation that is required for RNase H cleavage. The latter stems from the fact that the poly-rA/dT tract is rigid, and its deformations into an RNase H cleavage conformation lead to the base-pair slippage of its sequence. Our results demonstrated an unexpected mechanism by which the specific dynamic properties of the poly-rA/dT segment are involved in PPT recognition. The studies of HIV-1 RT have been performed in collaboration with Prof. Jarosław Poznański (IBB, Polish Academy of Sciences), the group of Jiri Šponer form Academy of Sciences of the Czech Republic, and the group of Taekjip Ha from Johns Hopkins University (Figiel et al., *J Biol Chem*, 2018).

Laboratory of Protein Metabolism in Development and Aging

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CURRICULUM VITAE

DEGREES

2009	PhD in Biological Engineering and Agronomic Sciences at the Institute of Life Sciences, Molecular Physiology Group (FYMO), Catholic University of Louvain, Belgium
2006	Master of Advanced Science in Biological Engineering and Agronomic Sciences at the Catholic University of Louvain, Belgium
2004	MSc in Microbiology at the University of Wrocław, Poland

RESEARCH EXPERIENCE

2017-Present	Head of Laboratory of Protein Metabolism in Development and Aging, IIMCB, Warsaw, Poland
2009-2017	Postdoctoral fellow at the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Germany
2004-2008	PhD studies at the Institute of Life Sciences, Molecular Physiology Group (FYMO), Catholic University of Louvain, Belgium

HONORS, PRIZES, AND AWARDS

2018	FIRST TEAM, Foundation for Polish Science
2018	EMBO Installation Grant
2017	OPUS, National Science Centre
2005	PhD Fellowship from the FNRS-Fund for Scientific Research, Belgium
2004	ERASMUS Scholarship

SELECTED PUBLICATIONS

Koyuncu S, Saez I, Lee HJ, Gutierrez-Garcia R, **Pokrzywa W**, Fatima A, Hoppe T, Vilchez D. The ubiquitin ligase UBR5 suppresses proteostasis collapse in pluripotent stem cells from Huntington's disease patients. ***Nat Commun***, 2018; 9(1): 2886

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* co-first authorship

DESCRIPTION OF CURRENT RESEARCH

The proteome is defined as the entire set of proteins that are expressed in a given cell type or organism, which can vary with time and physiological status. Quality control networks support the integrity of the cellular proteome. The human protein homeostasis network (proteostasis) involves >1000 accessory factors and regulatory components that govern protein synthesis, folding, and degradation. Defective folding can result in a greater abundance of toxic protein aggregates, which can endanger the integrity of the entire proteome. With age, the ability of post-mitotic cells to maintain a stable proteome is gradually compromised, particularly by the downregulation of molecular chaperones and lower efficiency of protein degradation. As such, impairments in proteostasis are a major hallmark of aging and associated with dementia, neurodegeneration, type 2 diabetes, cystic fibrosis, cancer, and cardiovascular disease (Labbadia and Morimoto, *Annu Rev Biochem*, 2015). One of the central nodes of the eukaryotic proteostasis network is the interaction between molecular chaperones and proteolytic machinery. To maintain the cellular proteome, molecular chaperones and ubiquitin-dependent degradation pathways coordinate protein refolding and the removal of terminally damaged proteins. Irreversibly affected proteins are recognized by chaperone-assisted E3 ubiquitin ligases, which target them for degradation by the ubiquitin-proteasome system (UPS) or autophagy (Fig. 1). Our studies concentrate on the basic understanding of the spatiotemporal regulation of protein quality control activity and processing of its substrates. In our research, we use a combination of biochemical, microscopic, and genetic techniques with tissue-specific approaches in *C. elegans*.

WE FOCUS MAINLY ON THE FOLLOWING PROJECTS:

Identification of signals that coordinate the function of distinct E3 ligases

The UPS is a major proteolytic route that maintains the proteome during development, stress, and aging. The 26S proteasome mainly mediates protein degradation upon the covalent attachment of ubiquitin to target proteins by E1 (activating), E2 (conjugating), and E3 (ligating) enzymes in the ubiquitylation process. Despite many structurally unrelated substrates, ubiquitin conjugation is remarkably selective. E3 ubiquitin ligases represent the largest group of proteins within the UPS, which is linked to their crucial role in substrate selection. A detailed analysis of several classes of E3 ligases identified specific proteins and molecular pathways that they regulate.

Furthermore, the heterotypic oligomerization of E3 ligases might control the specificity and processivity of ubiquitylation. Recently, Scott et al. (*Cell*, 2016) reported that two distinctive E3s could reciprocally monitor each other for the simultaneous and joint regulation of substrate ubiquitylation. Cullin-RING (CRL) ligase was shown to associate with a mechanistically distinct thioester-forming RBR-type E3, ARIH1, and rely on ARIH1 to directly add ubiquitin chains on CRL substrates. Therefore, the existence of cooperation between various E3 enzymes that increases their molecular capabilities appears to be highly probable but requires further exploration. Our long-term objective is to understand the mechanistic and developmental aspects of protein degradation pathways that are defined by a specific pair of E3 enzymes.

Regulation of methionine metabolism by the ubiquitin-proteasome system

S-adenosyl-L-methionine (SAM)-dependent methylation is central to the regulation of many biological processes, including gene expression, signaling, protein synthesis, and lipid metabolism. SAM is synthesized in the cytosol of every cell from L-methionine and ATP in a reaction that is catalyzed by methionine adenosyltransferase (Fontecave et al., *Trends Biochem*, 2004). Despite fundamental roles of the SAM cycle in a broad range of biological processes, the mechanisms of its regulation are still enigmatic. Our preliminary studies suggest that the UPS regulates SAM cycle activity. Our aim is to understand the ways in which the UPS modulates methionine metabolism, methylation potential of the cell, and epigenetic memory using *C. elegans* as an animal model. We believe that our research will also have broad implications for understanding the regulation of methionine metabolism in health and disease.

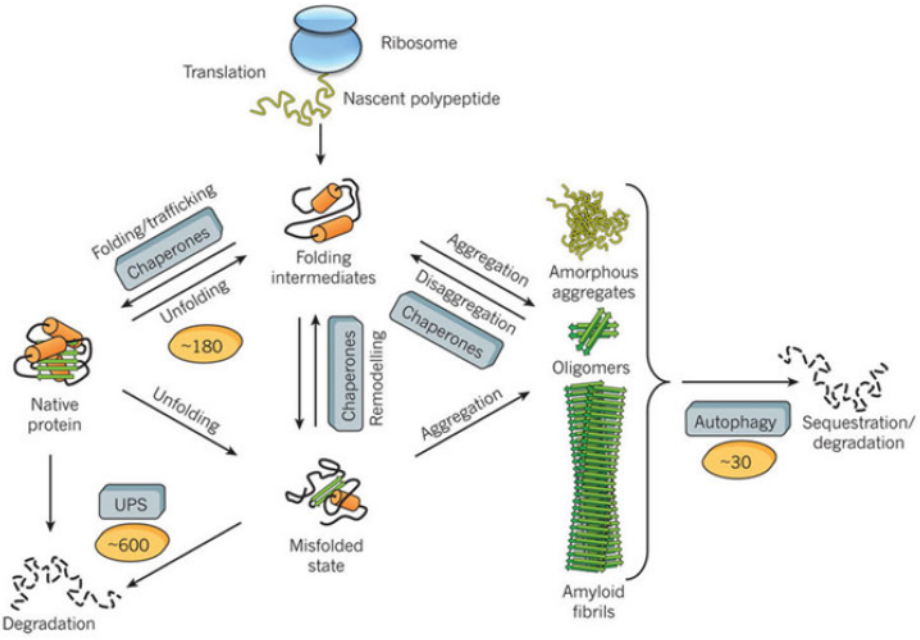

Fig. 1 The proteostasis network integrates chaperone pathways for the folding of newly synthesized proteins, for the remodeling of misfolded states, and for disaggregation with protein degradation that is mediated by the UPS and autophagy system. Approximately 180 different chaperone components and their regulators orchestrate these processes in mammalian cells, whereas the UPS comprises ~600 different components, and the autophagy system comprises ~30 different components. Figure from Harlt et al., *Nature*, 2011.

Stress-induced myosin folding and assembly mechanisms (Part Research Unit 2743 - Mechanical Stress Protection, financed by the German Research Foundation [DFG])

The assembly and maintenance of myofilaments require a tightly balanced proteostasis network. One key player in myosin organization and muscle thick-filament formation in health and disease is the Hsp90 co-chaperone UNC-45. The activity and assembly of various myosin subtypes are coordinated by conserved UCS (UNC-45/CRO1/She4p) domain proteins. One founding member of the UCS family is *Caenorhabditis elegans* UNC-45, a protein that is essential for the organization of striated muscle filaments (Price et al., *J Cell Sci*, 2002). Moreover, UNC-45 homologs exist in vertebrates, indicating a conserved requirement for myosin-specific co-chaperones (Price et al., *J Cell Sci*, 2002). Indeed, abnormal UNC-45 function is associated with severe muscle defects that result in skeletal and cardiac myopathies (Janiesch et al., *Nat Cell Biol,* 2007).

The integrity of sarcomeric structures is permanently challenged upon muscle growth and mechanical stress. In response to eccentric exercise or damage to myofibers, UNC-45 and the chaperone Hsp90 shuttle between the impaired myofibers to support their repair (Fig. 2). However, little is known about the coordination of protein homeostasis pathways upon mechanical stress. Therefore, the long-term objective of this project is to understand the ways in which the balance between protein folding and degradation networks is coordinated with myosin assembly and muscle integrity. We combine genetic and biochemical approaches to study the conserved function of UNC-45 in myosin assembly and examine the ways in which this function is modulated during mechanical stress. Specifically, we plan to use targeted screening strategies to uncover mechanosensory proteins, chaperones, and UPS and autophagy components that are required for muscle function. The conserved regulation of proteostasis networks is studied in *C. elegans*, C2C12 mouse myoblasts, and human skeletal muscles. Finally, we want to investigate the remodeling of UNC-45 folding machinery under conditions of mechanical stress. A combination of genetic, biochemical, and *in vivo* imaging techniques will allow us to examine stress-induced changes in protein folding and degradation pathways.

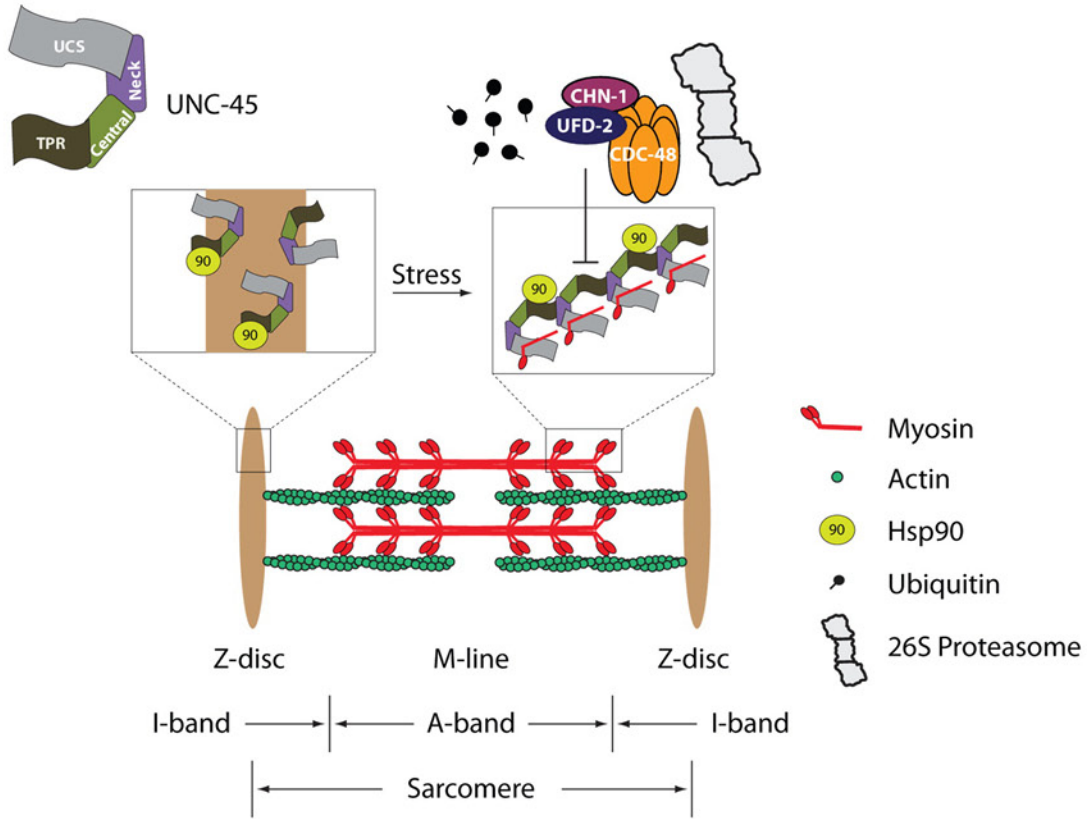

Fig. 2 Model for the UNC-45 polymerization in response to stress. The sarcomeric unit is defined by the distance between two Z-discs including the A-band, I-band, and M-line. UNC-45 composes tandem modules that allow the simultaneous binding of Hsp70/Hsp90 and myosin, enabling the folding and assembly of myosin in regular spacing. In the fully developed muscle, monomeric UNC-45 might be stored at the Z-disk, which anchors the thin actin filaments of the I-band. Under stress conditions, UNC-45 is relocated to damaged myosin filaments of the A-band and might assemble into short chaperone chains to maintain the sarcomeric structure especially during muscle regeneration and aging. The conserved CDC-48/UFD-2/CHN-1 ubiquitylation complex might influence the process of UNC-45 chain formation. The ubiquitylation of UNC-45 either reduces the pool of the monomeric form available for chain formation or inhibits UNC-45 polymerization directly by modifying the binding interface. Figure adapted from Pokrzywa and Hoppe, *Worm*, 2013.

Laboratory of Zebrafish Developmental Genomics Max Planck/IIMCB Research Group

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CURRICULUM VITAE

DEGREES

2009	PhD in Biology, Department of Biological Sciences, National University of Singapore
2004	BSc (Hons.) in Biology, Department of Biological Sciences, National University of Singapore

RESEARCH EXPERIENCE

2014-Present	Head, Zebrafish Developmental Genomics Laboratory, Max Planck/IIMCB Research Group, Warsaw, Poland
2013-2014	Research Associate, Genome Institute of Singapore; 2013 Research visit, laboratory of Prof. Peter Alestrom, Norwegian School of Veterinary Sciences, Oslo, Norway
2009-2013	Postdoctoral Fellow with Dr. Sinnakaruppan Mathavan, Genome Institute of Singapore
2004-2009	Doctoral research with Profs. Gong Zhiyuan and Vladimir Korzh, Department of Biological Sciences, National University of Singapore

HONORS, PRIZES, AND AWARDS

2016	FIRST TEAM, Foundation for Polish Science
2016	OPUS (as a partner), National Science Centre
2014	OPUS, National Science Centre
2000-2004	ASEAN Undergraduate Scholarship
2003	Science Faculty Dean's List, National University of Singapore

SELECTED PUBLICATIONS

IIMCB Best Papers Award

Pawlak M, **Kedzierska KZ**, **Migdal M**, Nahia KA, Ramilowski JA, Bugajski L, Hashimoto K, **Marconi A**, Piwocka K, Carninci P, **Winata CL**. Dynamics of cardiomyocyte transcriptome and chromatin landscape demarcates key events of heart development. ***Genome Res***, 2019 Mar;29(3):506-519

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^Winata CL, Korzh S, Kondrychyn I, Korzh V, Gong Z. The role of vasculature and blood circulation in zebrafish swimbladder development. ***BMC Dev Biol***, 2010; 10:3

Yin A, **^Winata CL**, Korzh S, Korzh V, Gong Z. Expression of components of Wnt and Hedgehog pathways in different tissue layers during lung development in *Xenopus laevis*. ***Gene Expr Patterns***, 2010; 10(7-8):338-344

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^ no IIMCB affiliation

*equal contribution

DESCRIPTION OF CURRENT RESEARCH

The aim of our research is to understand the mechanism of gene regulation during embryonic development *in vivo* using zebrafish (*Danio rerio*) as a model organism. Our main research interests center around the regulation of gene expression in embryonic development. In particular, we seek to understand the mechanism by which transcription factors (TFs) and the chromatin landscape interact to regulate the development of an organ. We also investigate the biological consequences of post-transcriptional modifications on maternal mRNAs, including cytoplasmic polyadenylation and RNA editing.

SELECTED HIGHLIGHTS

Elucidating the genome-wide regulatory landscape of heart development

Our main line of research attempts to understand the mechanism of transcriptional regulation through interactions between TFs and the epigenetic landscape in heart development and disease. Although the heart in different species of vertebrates can have two to four chambers, the step-wise morphogenesis of progenitor specification, migration, tube formation, and looping has been shown to be highly conserved. To gain a comprehensive view of the gene regulatory network in heart development, we investigate two distinct cell types of the heart: cardiomyocytes (CMs) and cardiac pacemaker cells. These two cell types originate from the same progenitor population but are set apart early in the course of heart development through induction of the expression of distinct TFs, resulting in their different properties. The parallel studies in these two cell types will provide an additional interesting dimension of differential gene regulation in the context of cell type specification.

Transcriptional regulatory landscape in developing cardiomyocytes

Heart muscle cells or CMs are specified early during embryogenesis from a pool of mesodermal progenitors. To elucidate the dynamics of the transcriptional regulatory landscape during heart development, we employed a combination of transcriptome profiling (RNA-seq) and an assay for chromatin accessibility (ATAC-seq) at several key stages of heart development. In collaboration with K. Piwocka (Nencki Institute, Poland) and P. Carninci (RIKEN Center for Integrative Medical Sciences, Japan), we isolated CMs from zebrafish transgenic lines with CM-specific green fluorescent protein (GFP) expression and performed RNA-seq to profile transcriptome dynamics across three developmental stages. In collaboration with Piero Carninci (RIKEN Center for Life Science Technologies, Japan), we performed bioinformatics analyses of the RNA-seq data. We also performed ATAC-seq to profile the chromatin accessibility regions in samples that were stage-matched to the RNA-seq experiment. Our analyses revealed genetic regulatory hubs that drive crucial events of heart development, which contained key cardiac TFs and are associated with open chromatin regions that are enriched for DNA sequence motifs that belong to the family of the corresponding TFs. Loss of function of the cardiac TFs Gata5, Tbx5a, and Hand2 affected the cardiac regulatory networks and caused global changes in the chromatin accessibility profile. Among the regions with differential chromatin accessibility in mutants were highly conserved non-coding elements that represent putative enhancers that drive heart development. Our results revealed the dynamic regulatory landscape throughout heart development and identified interactive molecular networks that drive key events of heart morphogenesis.

At the core of the machinery that regulates each step of heart morphogenesis are cardiac TFs, including Nkx2.5, Gata5, Tbx5, and Hand2. These TFs are known to play a role in establishing the CM identity of mesodermal progenitor cells, regulating the formation and looping of the heart tube and the specification of atrial and ventricular CMs. To characterize the molecular mechanism and downstream regulatory network of cardiac TFs, we applied in silico TF footprinting methodology to our ATAC-seq data to identify genome-wide binding sites of Nkx2.5, Gata5, Tbx5, and Hand2 during key phases of heart development. Ultimately, we aim to characterize the contribution of the dynamic transcriptional regulatory landscape to heart development and identify novel elements (both genic and non-genic) that are associated with heart defects.

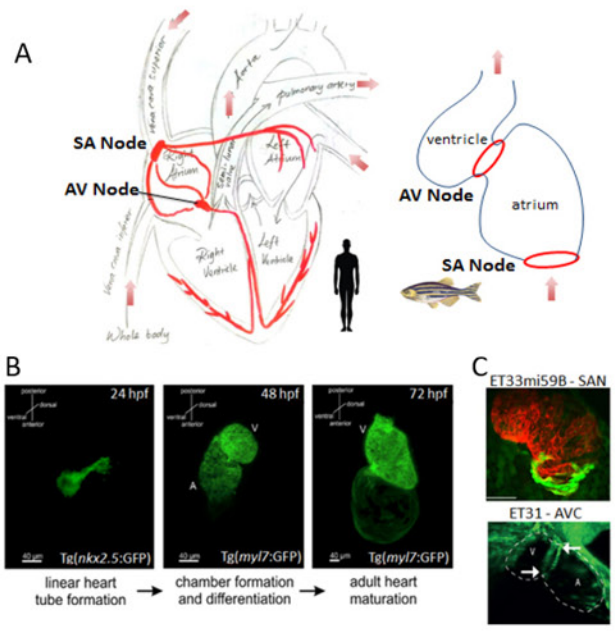


Fig. 1 (A) The rhythmic contraction of the heart is regulated by the cardiac conduction system (CCS), which consists of two major pacemakers: the sinoatrial node (SAN) and atrioventricular node (AVN). These pacemaker cells are set apart from cardiomyocytes early in the course of heart development through the initiation of distinct molecular programs. (B) Stepwise process of heart development in the zebrafish. (C) Pacemaker cells expressing GFP in the zebrafish transgenic lines ET33mi59B and ET31.

Genomicsdissection of pacemaker development

The cardiac conduction system is responsible for generating and propagating the electrical impulses that are required for the contraction of heart muscle tissues. The cardiac conduction system consists of pacemaker cells, specialized heart muscle cells that serve to ensure rhythmic contractions of the heart. Pacemaker cells possess distinctive morphological and electrophysiological properties that are specialized for their function. They are set apart early from CMs in the course of heart development through induction of the expression of core TFs, such as Tbx2, Tbx3, Tbx18, and Isl1, which prevents their differentiation into CMs. Once specified, pacemaker progenitor cells further develop low conductance properties through the expression of gap junction proteins that are distinct from CMs. Despite the knowledge of key genetic factors that are required for pacemaker cell specification, the molecular mechanisms that regulate their development are still insufficiently understood. Important questions remain with regard to the ways in which the underlying molecular mechanism translates into the proper functioning of pacemaker cells and the consequences of their dysregulation. Moreover, inherited forms of arrhythmia are often associated with more common forms of congenital heart malformations that affect other tissue types of the heart, including CMs, implying interconnectivity of the gene regulatory networks that govern their development and function.

The zebrafish heart exhibits remarkable similarities to the human heart in terms of basal heart rate, electrophysiological properties, and action potential shape and duration. Thus, it is an ideal model organism to study the heart pacemaker and model human clinical conditions that affect pacemaker function. Importantly, zebrafish have the potential to allow large-scale pharmaceutical screening to discover new therapies for heart disease, particularly those that affect the pacemaker. In collaboration with Vladimir Korzh (IIMCB), we utilized the transgenic lines ET33mi59B, ET33mi28, and ET31, which express GFP in subpopulations of pacemaker cells, to characterize the morphology of the zebrafish pacemaker and isolate pacemaker cells for further genomic analyses to elucidate gene regulatory networks in pacemaker development. Transcriptome profiling of isolated pacemaker cells revealed distinct molecular profiles that defined CMs and pacemaker cells, providing important insights into the mechanism of their diversification. Future efforts will focus on identifying the regulatory pathways that underlie pacemaker development and function. Ultimately, we aim to establish zebrafish as a model for pacemaker dysfunction through the identification of novel genetic elements that may be implicated in pacemaker-related human diseases and the generation of new mutant lines for functional studies of these factors.

Developmental control through the post-transcriptional regulation of maternal mRNA expression

During embryogenesis, a silent transcriptional period exists from the moment of fertilization to the time of zygotic genome activation, known as the mid-blastula transition (MBT) in zebrafish and frogs. During this period of transcriptional silence, development is regulated by maternally deposited mRNAs that undergo various forms of posttranscriptional modifications to regulate their expression.

Translational control by cytoplasmic polyadenylation

Maternal mRNAs are initially deposited in the immature oocyte in a translationally dormant state, with a very short poly(A) tail. Two major waves of cytoplasmic polyadenylation occur during oocyte maturation and upon fertilization, resulting in the translational activation of distinct subpopulations of maternal mRNAs. Through profiling of the polysome-associated transcriptome, we discovered that cytoplasmically polyadenylated maternal mRNAs are increasingly associated with polysomes, which demonstrates the coupling of translation to cytoplasmic polyadenylation. Furthermore, we found that the translational regulation of maternal mRNAs by cytoplasmic polyadenylation is required for the progression of embryonic development by ensuring the activation and clearance of key factors that determine zygotic genome activation. Thus, we established cytoplasmic polyadenylation as a prominent mode of the temporal activation of maternal mRNAs that is necessary for MBT (Winata et al., *Development*, 2018).

Current work in the laboratory focuses on studying the mechanistic basis of cytoplasmic polyadenylation through functional analyses of cytoplasmic polyadenylation element binding proteins (CPEBs) that are known to regulate cytoplasmic polyadenylation and translation. The transcripts of at least three different CPEBs (cpeb1b, cpeb4a, and cpeb4b) are present as maternal mRNAs and associated with polysomes between fertilization and MBT. Functional studies of these CPEBs are currently underway, and we are developing methods and tools for the analysis of RNA binding by these factors in the form of CRISPR-generated transgenic lines.

RNA editing of maternal mRNAs

RNA editing refers to the post-transcriptional modification of RNA sequences, the most common form of which is A-to-I conversion that occurs through the deamination of adenosine (A) at the C6 position, converting it to an inosine (I). In humans, the misregulation of A-to-I RNA editing in somatic tissues may lead to neurological and metabolic disorders, autoimmune diseases, and cancer. A mode of post-transcriptional gene regulation, such as RNA modification, would nicely fit into the scenario that occurs at the earliest stages of embryonic development, during which the embryo contains an abundant supply of maternal mRNAs and zygotic transcription is still absent. Surprisingly, despite this, RNA editing has been seldom considered in the context of embryonic development. In collaboration with the Bochtler laboratory (IIMCB), we aim to elucidate the biological function of A-to-I RNA editing in early embryonic development using zebrafish as a model organism.

Two paralogs of the A-to-I RNA editing enzyme, adar and adarb1, are present in the form of maternally deposited transcripts at the earliest stages of development (Winata et al., *Development*, 2018). We conducted a pilot study in which we sequenced the genomes of a pair of adult zebrafish and transcriptomes of their embryonic offspring. To reliably detect RNA editing events, we developed a new and improved method for RNA editing discovery. Our preliminary analyses confirmed the presence of RNA editing in both maternally deposited and zygotic transcripts. We identified ~19,000 sites in the transcriptome of each stage, and the majority of these were stage-specific, suggesting that RNA editing may play a role in early embryogenesis. Currently, we have generated a zebrafish mutant line for the adar gene using CRISPR/Cas9. This line will be used for more detailed functional studies of RNA editing. Furthermore, in collaboration with the Bujnicki laboratory (IIMCB), we are also planning to identify a correlation between RNA editing and structure through the prediction of secondary structures in conserved domains in selected mRNA candidates that will be identified through comparative transcriptome analyses with several closely related fish species from the Carp family. The transcriptome profiling and de novo assembly of these related species of fish are ongoing and promise to be a valuable resource for various fields of study.

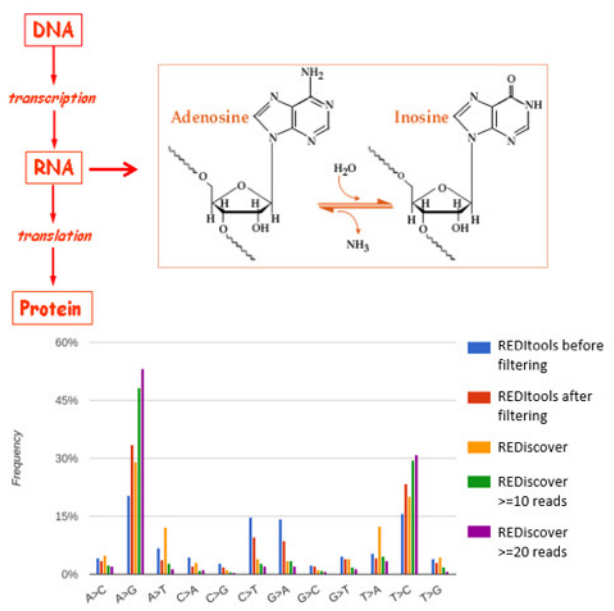
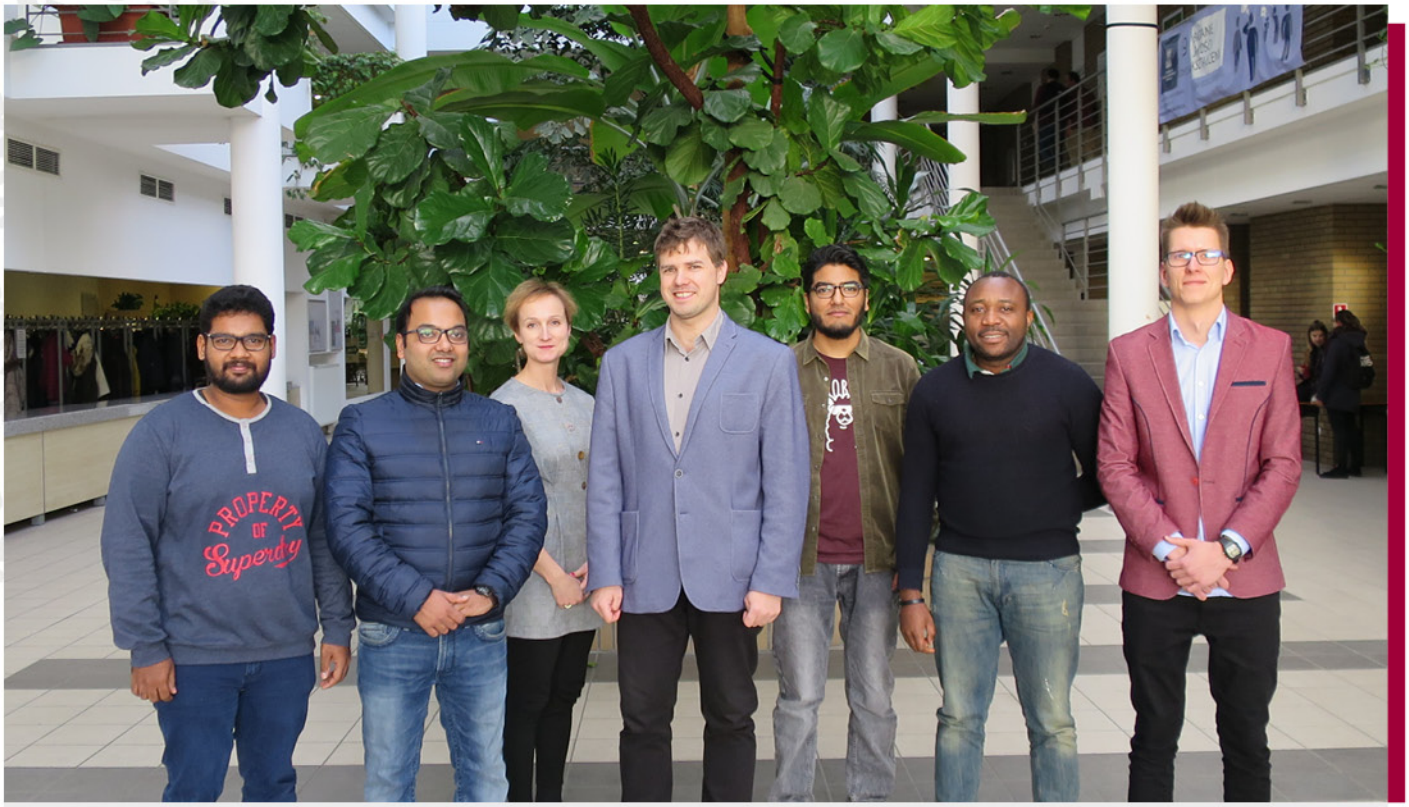


Fig. 2 RNA editing alters the sequence of RNA through conversion of adenosine to inosine. We plotted the frequency of RNA editing changes detected in the transcriptome of the early zebrafish embryo by existing tool (REDItools) and our new algorithm (REDiscover). In RNA-seq data, A-to-I editing can be detected as a, A-to-G or T-to-C conversion from the reference sequence.



Laboratory of Biomolecular Interactions and Transport AMU/IIMCB in Poznań

GROUP MEMBERS

Lab Leader
Jan Brezovsky, PhD

Postdoctoral Researchers
Cedrix Jurgal Dongmo Foumthuim, PhD (since October 2018)
Nikhil Agrawal, PhD (since November 2018)

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Carlos Eduardo Sequeiros Borja, MSc
Bartłomiej Surpeta, MSc
Aravind Selvaram Thirunavukkarasu, MSc (since November 2018)
Dheeraj Kumar Sarkar, MSc (AMU, since December 2018)

Research Assistant
& Laboratory-Administratvie Partner
Katarzyna Voelkel (since September 2018)

LAB LEADER

Jan Brezovsky, PhD

CURRICULUM VITAE

DEGREES

2011	PhD in Environmental Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic
2007	MSc in Biophysics, Faculty of Science, Masaryk University, Brno, Czech Republic

RESEARCH EXPERIENCE

2016-Present	Head of the joint Laboratory, International Institute of Molecular and Cell Biology in Warsaw, and Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University in Poznań, Poland
2016	Assistant Professor, Department of Experimental Biology, Masaryk University, Brno, Czech Republic
2015-2016	Postdoctoral Researcher, International Clinical Research Center of St. Anne's University Hospital, Brno, Czech Republic
2014	Research visit to the group of Professor Rebecca Wade, Heidelberg Institute of Theoretical Science, Germany
2012-2016	Leader of Research Team, Loschmidt Laboratories, Faculty of Science, Masaryk University, Czech Republic
2009-2011	Research Assistant, Loschmidt Laboratories, Department of Experimental Biology, Faculty of Science, Masaryk University, Brno, Czech Republic
2007-2008	Research Assistant, National Centre for Biomolecular Research, Faculty of Science, Masaryk University, Brno, Czech Republic

HONORS, PRIZES, AND AWARDS

2018	SONATA BIS, National Science Centre
2017	OPUS, National Science Centre
2016	GACR grant from Czech Science Foundation
2015-2016	Elected member of the national node committee of European Life-Science Infrastructure for Biological Information, Czech Republic (ELIXIR-CZ)
2011	5th place at national competition Chemistry Prize of Jean-Marie Lehnen
2011	Dean's prize for outstanding PhD research, Masaryk University, Brno, Czech Republic
2007	Research grant from Masaryk University, Brno, Czech Republic

SELECTED PUBLICATIONS

Jurcik A, Bednar D, Byska J, Marques SM, Furmanova K, Daniel L, Kokkonen P, **Brezovsky J**, Strnad O, Stourac J, Pavelka A, Manak M, Damborsky J, Kozlikova B. CAVER Analyst 2.0: Analysis and Visualization of Channels and Tunnels in Protein Structures and Molecular Dynamics Trajectories. ***Bioinformatics***, 2018; 34(20):3586-88

Grulich M, **Brezovsky J**, Stepanek V, Palyzova A, Maresova H, Zahradnik J, Kyslikova E, Kyslik P. In-silico driven engineering of enantioselectivity of a penicillin G acylase towards active pharmaceutical ingredients. ***J Mol Catal B Enzym***, 2016; 133, Supplement 1:S53-S59

^Brezovsky J*, Babkova P*, Degtjarik O, Fortova A, Gora A, Iermak I, Rezacova P, Dvorak P, Smatanova IK, Prokop Z, Chaloupkova R, Damborsky J. Engineering a de novo transport tunnel. ***ACS Catal,*** 2016; 6(11):7597-610

Bendl J, Musil M, Stourac J, Zendulka J, Damborsky J, **^Brezovsky J#**. PredictSNP2: A unified platform for accurately evaluating SNP effects by exploiting the different characteristics of variants in distinct genomic regions. ***PLoS Comput Biol,*** 2016; 12(5):e1004962

Bendl J, Stourac J, Sebestova E, Vavra O, Musil M, **^Brezovsky J#**, Damborsky J#. HotSpot Wizard 2.0: automated design of site-specific mutations and smart libraries in protein engineering. ***Nucleic Acids Res,*** 2016; 44:W479-487

Daniel L, Buryska T, Prokop Z, Damborsky J, **^Brezovsky J#.** Mechanism-based discovery of novel substrates of haloalkane dehalogenases using in silico screening. ***J Chem Inf Model,*** 2015; 55(1):54-62

Sykora J*, **^Brezovsky J***, Koudelakova T*, Lahoda M, Fortova A, Chernovets T, Chaloupkova R, Stepankova V, Prokop Z, Smatanova IK, Hof M, Damborsky J. Dynamics and hydration explain failed functional transformation in dehalogenase design. ***Nat Chem Biol,*** 2014; 10(6):428-430

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Prokop Z*, Sato Y*, **^Brezovsky J***, Mozga T, Chaloupkova R, Koudelakova T, Jerabek P, Stepankova V, Natsume R, Leeuwen JGE, Janssen DB, Florian J, Nagata Y, Senda T, Damborsky J. Enantioselectivity f Haloalkane Dehalogenases and its Modulation by Surface Loop Engineering. ***Angew Chem Int Ed Engl,*** 2010; 49(35):6111-15

* equal contribution

\# corresponding author

^ no IIMCB affiliation

DESCRIPTION OF CURRENT RESEARCH

Research in our laboratory is oriented toward answering fundamental questions about the mechanism of action of various proteins that have biomedical and biotechnological importance. We investigate the mechanisms that enable the migration of ligands to and from functional sites that are deeply buried within protein structures. We also explore the implications of such processes for the functions of living cells. To achieve these goals, we develop new computational protocols and tools and apply them to the analysis of biomedically and biotechnologically relevant proteins.

At any given moment, living systems contain several thousand small organic molecules, both endogenous and exogenous, comprising the metabolome. To exert their function, the hosts of molecules need to arrive at their sites of action, mostly represented by protein surfaces and internal cavities. The transport of the metabolome is largely governed by protein tunnels and channels (Fig. 1). Such tunnels and channels secure the transport of ligands between different regions and connect inner protein cavities with the protein surface, connect two or more different cavities, or connect even different cellular environments, such as in membrane proteins. The presence of very sophisticated transport processes markedly contributes to the symbiotic co-existence of individual chemical species within a single compartment or whole cell without the presence of overly disruptive interference. Protein channels facilitate the regulated and very selective transport of ions and ligands across a membrane between different cellular compartments. The role of channels in the function of various proteins has been the focus of intense research for years. Their importance is illustrated by many diseases that are caused by channel mutations. Such channel pathologies can severely impair

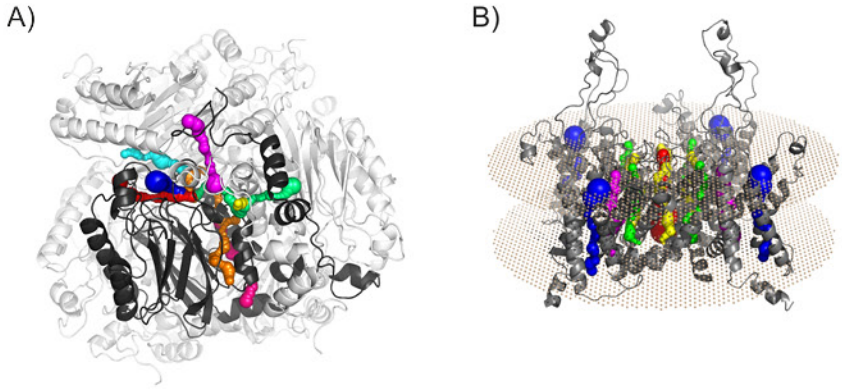


Fig. 1 Illustrative examples of protein tunnels and channels. (A) Putative tunnels in aliphatic amidase AmiE. The analyzed monomer is depicted in the black cartoon. The remaining five monomers are depicted in the white cartoon. The tunnels are shown as colored spheres. (B) Channels (pores) in voltage-gated potassium channel protein. The central pore is shown as red spheres. The prospective alternative pores are shown as blue, green, yellow, and magenta spheres.

the function of many physiological systems, manifested as various diseases, including epilepsy, hypertension, cystic fibrosis, diabetes, and cancer. To counteract these malfunctions, many inhibitors or activators that affect transport through these channels have been identified.

Tunnels connect buried functional sites to the bulk solvent, enabling the access of substrates and release of products. Moreover, the tunnels are responsible for many additional functions that are essential for the proper actions of proteins that are exposed to interference from individual species that are present in the metabolome of the living cell. The tunnels enable the access of preferred substrates and deny access to non-preferred substrates. The tunnels can prevent damage to enzymes that contain transition metals through ligation and damage to the cell that is caused by the release of toxic intermediates to the cellular environment. The tunnels also enable reactions that require the absence of water and allow the temporal and spatial synchronization of reactions. Most enzymes likely possess tunnels. In fact, the presence of tunnels was already described for enzymes from six Enzyme Commission classes and four structural classes of proteins. In many cases, tunnels are transient, meaning they cannot be readily identified from static crystal structures. Therefore, we can expect the discovery of tunnels in many other protein families. Recognizing the importance of transport processes for enzymatic catalysis, many protein engineering studies have successfully modified tunnels to improve enzymatic activity, specificity, enantioselectivity, and stability. Tunnels were established as critical functional factors in enzyme catalysis relatively recently, and their role in cellular biochemistry and tunnel mutations in disease etiology has been largely overlooked. However, many enzymes that are known to contain tunnels have been associated with the development of various ailments, including cancer, neurodegenerative disorders, autoimmune diseases, and inflammation. Inhibitors of some of these enzymes have been shown to bind to tunnels exclusively, thus confirming the proposed role of tunnels in disease etiology and treatment.

To fill the gaps in our knowledge of ligand transport phenomena, we are currently focusing on the following:

Enabling routine and reliable analysis of transient transport tunnels in proteins

The primary goal of this project is to enable large-scale studies of properties and dynamics of functionally relevant transport tunnels. We are currently evaluating and optimizing various approximate dynamics methods to provide ensembles of protein structures with tunnel properties and dynamics that correspond to the those that are obtained from rigorous simulations. In the next step, we will utilize the developed and thoroughly validated method for the detection of transient tunnels in all proteins with buried functional cavities with available 3D structures. The biologically relevant tunnels that are identified in these proteins will extend our fundamental knowledge about the properties that determine the transport component of protein function. We believe that the results of this large-scale analysis will stimulate further investigations of transient tunnels and their gates and enable the targeting of transient tunnels in protein engineering and drug discovery efforts.

Understanding molecular origins of mechanisms that govern functions of enzymes with buried actives sites

The primary goal of this research is to unveil molecular bases of largely unexplored factors that notably affect the biological function of enzymes with buried active sites (i.e., substrate inhibition, cooperativity and interference between molecules of substrates and products during their simultaneous transport via the tunnels; Fig. 2). We are working on comprehensive kinetics models of ligand transport in enzymes that will enable us to perform detailed analyses of structure-dynamics-function relationships that govern the transport of multiple ligands via the tunnels, revealing roles of direct interactions among ligands and allosteric effects on the tunnels that are mediated by protein-ligand interactions. We expect to obtain novel insights into the origins of substrate inhibition and cooperativity (i.e., phenomena that are necessary for the proper in vivo functions of many enzymes). The knowledge that is obtained can then be exploited to target these properties in research that seeks to engineer better enzymes and develop novel inhibitors. Finally, the findings on mutual interference among different ligands and effects on their transport will facilitate more accurate studies of enzyme-drug association/dissociation processes, thus paving the way toward the optimization of drug residence times.

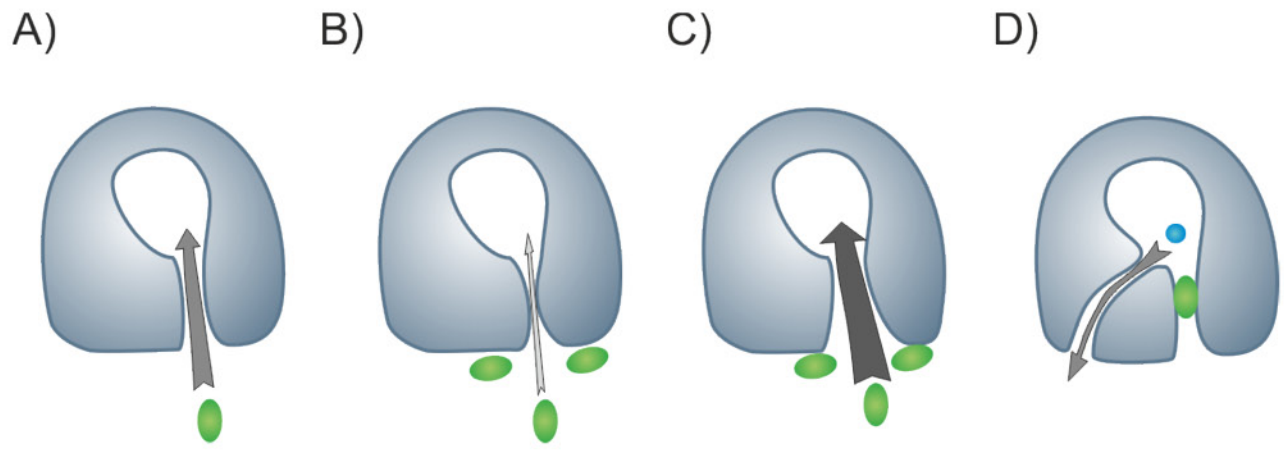


Fig. 2 Various mechanisms of molecular transport within the enzyme structure. (A) At a low concentration of substrate molecules, their transport can be considered isolated. At higher concentrations, the binding of additional molecules can directly or indirectly modulate the transport process, resulting in either (B) adverse effects (substrate inhibition) or (C) positive effects (cooperative action). (D) The binding or transport of one molecule can interfere with the transport of another, redirecting it via less preferred routes.

STRATEGIC PROGRAMMES

Auresine

Head
Izabela Sabała, PhD

Senior Scientist
Elżbieta Jagielska, PhD

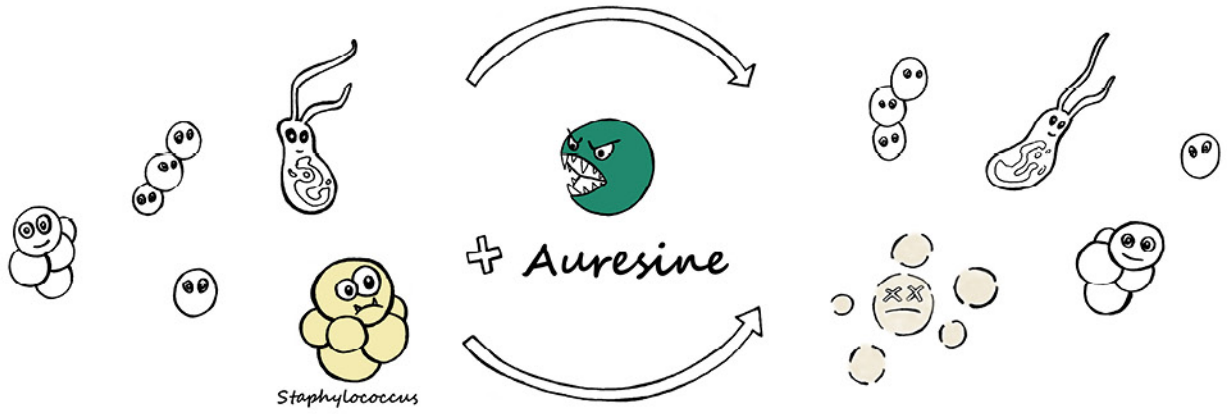
Postdoctoral Researcher
Piotr Małecki, PhD

PhD Students
Paweł Mitkowski, MSc
Alicja Wysocka, MSc

Technician
Weronika Augustyniak, MSc

MSc students
Piotr Bartosz
Karolina Trochimiak

MECHANISM OF ACTION



Weronika Augustyniak

Auresine is a peptidoglycan hydrolase – enzyme which recognizes staphylococcal cells (pentaglycine cross-bridges, characteristic component of staphylococcal peptidoglycan mesh) and cleaves it leading to instant disintegration of the cell walls and cell death.

RESEARCH FOCUS

Our research focuses on bacteriolytic enzymes that very selectively and effectively eliminate staphylococcal cells from various environments. We work on developing commercial applications for such enzymes, especially for the patented enzyme, Auresine®. These enzymes can be used in diagnostic tests, as a food bioprotectant, to decontaminate various surfaces in industry and hospitals, and as a component of hygiene products for animals and humans. Based on the results of our basic research, we are able to address very practical issues, such as the development of resistance, tolerance to environmental conditions, and protein stability. The structural and biochemical characterization of enzymes broadens our knowledge about the regulation of their activity and enzyme specificity and also provides a scientific basis for structure-designed enzyme engineering.

MAIN ACHIEVEMENTS IN 2018

We are conducting the TeamTech project (Foundation for Polish Science program), which focuses on developing new-generation wound dressings that are functionalized with bacteriolytic enzymes. We completed formation of the project team and the network of external experts who support our efforts in the area of nanomaterials.

We were awarded a grant from the International Academic Partnerships program, funded by the Polish National Agency for Academic Exchange (NAWA). The MolSpec project, "Molecular basis of enzyme specificity and applications," will be performed in collaboration with Trinity College Dublin (Ireland), the Applied Molecular Biosciences Unit of the Department of Life Sciences FCT-NOVA (Portugal), and the Fraunhofer Institute for Silicate Research (Germany).

Our team completed three Quest for Commercialization grants funded by IIMCB to leverage the commercialization of Auresine. They allowed us:

- to establish very simple and effective technology for the one-step, large-scale purification of our recombinant enzyme,
- to obtain international trademark protection for the name and graphic logo of Auresine®,
- to prepare a new, professional webpage that is dedicated to the Auresine project (www.auresine.com), illustrated by our technician Weronika Augustyniak.

We continue collaborations with our business partners to test the implementation of Auresine in industry and with a global supplier of R&D chemicals for the worldwide distribution of Auresine® (Merck-Sigma-Aldrich cat. no. SAE0083-1MG).

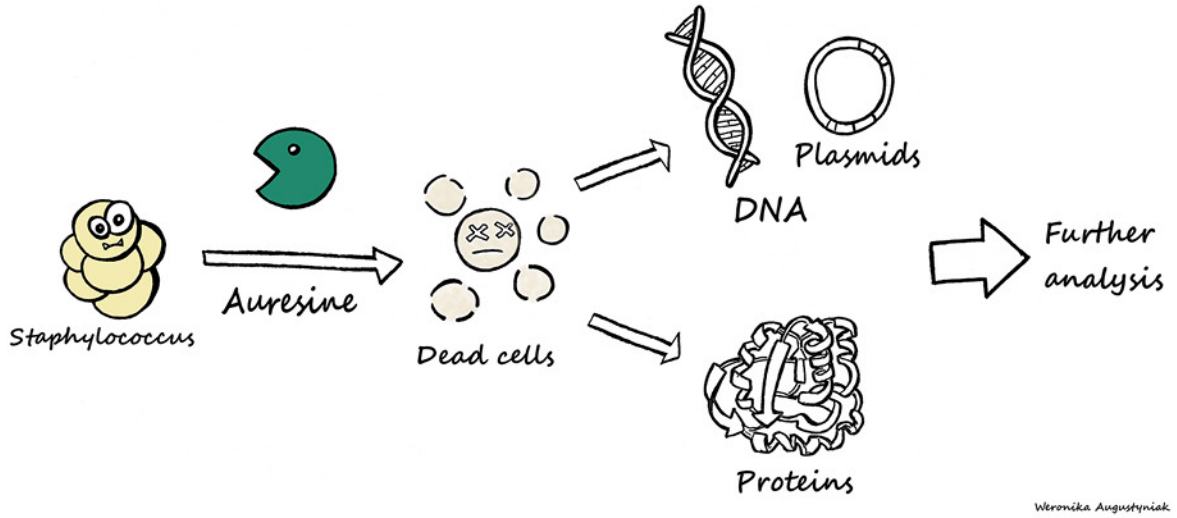
We established a collaboration with a global supplier of veterinary products that is interested in implementing our enzymes in their innovative products.

Our research has been presented at prestigious international meetings:

- EMBO Workshop on Bacterial Persistence and Antimicrobial Therapy, Ascona, Switzerland
- EMBO Workshop on Viruses of Microbes, Wrocław, Poland
- 18th International Symposium on Staphylococci and Staphylococcal Infection, Copenhagen, Denmark
- The Lysin Meeting: 2nd International Symposium on Antimicrobial Hydrolytic Enzymes, Rockefeller University, New York, USA
- Bessy User Meeting, 2018, Berlin, Germany

We summarized our latest results in paper: Mitkowski P, Jagielska E, Nowak E, Bujnicki JM, Stefaniak F, Niedziałek D, Bochtler M, Sabała I. Structural bases of peptidoglycan recognition by lysostaphin SH3b domain. *Sci Rep*. 2019 Apr 12;9(1):5965.

LABORATORY USE



Recombinant Auresine effectively digest cell walls of staphylococcal cells in unique conditions (water and low temperature) which prevent degradation of DNA or proteins during isolation procedure (now available from Sigma-Aldrich).

Auresine +48 22 5970 789 auresine@iimcb.gov.pl www.auresine.com

Study on Aging and Longevity

Head
Małgorzata Mossakowska, PhD, DSc Habil

Project Assistant
Aleksandra Szybalska, MSc

A study on aging and longevity was launched at IIMCB by the PolStu99 project that was commissioned by the Committee for Scientific Research (KBN), called "Genetic and environmental factors of longevity of Polish centenarians" (PolStu2001).

The PolSenior project, carried out in 2007-2012, was the largest gerontology research project in Poland and one of the largest in Europe. The results of PolSenior served as the basis for recommendations that were developed with regard to public health and social policies for the elderly population at both the national and local levels. A comprehensive approach to the problems of the aging population is consistent with the assumptions of policies that target senior citizens and provides a solid academic foundation for pursuing these policies. This project resulted in the detailed characterization of the elderly population in Poland and created a bank of biological samples and a database that includes all information from questionnaires and biochemical and genetic analyses. This enables comparisons with other studies and data gathering from projects that are conducted in other countries for pooled analyses of large populations.

In 2018, the PolSenior Study Group continued analyses of the collected data and published five articles:

- Szybalska et al. (*Eur Geriatr Med*, 2018),
- Szybalska et al. (*Arch Gerontol Geriatr*, 2018),
- Rewiuk et al. (*Exp Gerontol*, 2018),
- Mehr et al. (*Gerodontology*, 2018),
- Styszynski et al. (*J Physiol Pharmacol*, 2018).

Biological material that has been collected within the framework of the Polish Centenarians Project, PolSenior Project, and PLGen Project* has been further studied and led to three publications:

- Kocełak et al. (*Adv Med Sci*, 2018),
- Gutmajster et al. (J Appl Genet, 2018),
- Hamann et al. (*Gerontology*, 2019).

The group that is led by Dr. M. Mossakowska, in cooperation with other PolSenior consortium members, continues to investigate the prevalence of diabetes, anemia, and depression among Polish older adults and their health and socioeconomic covariates. It also continued its activities as a member of the NCD Risk Factor Collaboration (NCD-RisC). In 2018, a paper on trends and variations in raised blood pressure in the population of 88.6 million participants was published (NCD-RisC group, *Int J Epidemiol*, 2018).

The implementation of the PolSenior2 project, coordinated by the Medical University of Gdańsk, began in 2017, and the field work started in October 2018. Financial resources were obtained from the Ministry of Health. The study is being performed with the support and expertise of researchers who were involved in the PolSenior project that was led by IIMCB.

As a result of cooperation with the Polish Association Supporting People with Inflammatory Bowel Disease "J-elita" and Jagiellonian University Medical College and with support from the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), the study on the indirect costs of IBD has been extended to 11 European countries.

Full list of publications available on www.iimcb.gov.pl/en/research/publications/33-polsenior-project.

*PLGen Project - Polish Reference Genome for Genomic Diagnostics and Personalized Medicine (performed in 2013-2016)

CORE FACILITIES

Core Facility

Head
Alicja Żylicz, PhD, Professor

Vice Head
Roman Szczepanowski, PhD

Senior Staff Scientists
Matylda Macias, PhD (part-time)
Katarzyna Misztal, PhD
Krzysztof Skowronek, PhD, DSc Habil
Tomasz Węgierski, PhD (part-time)

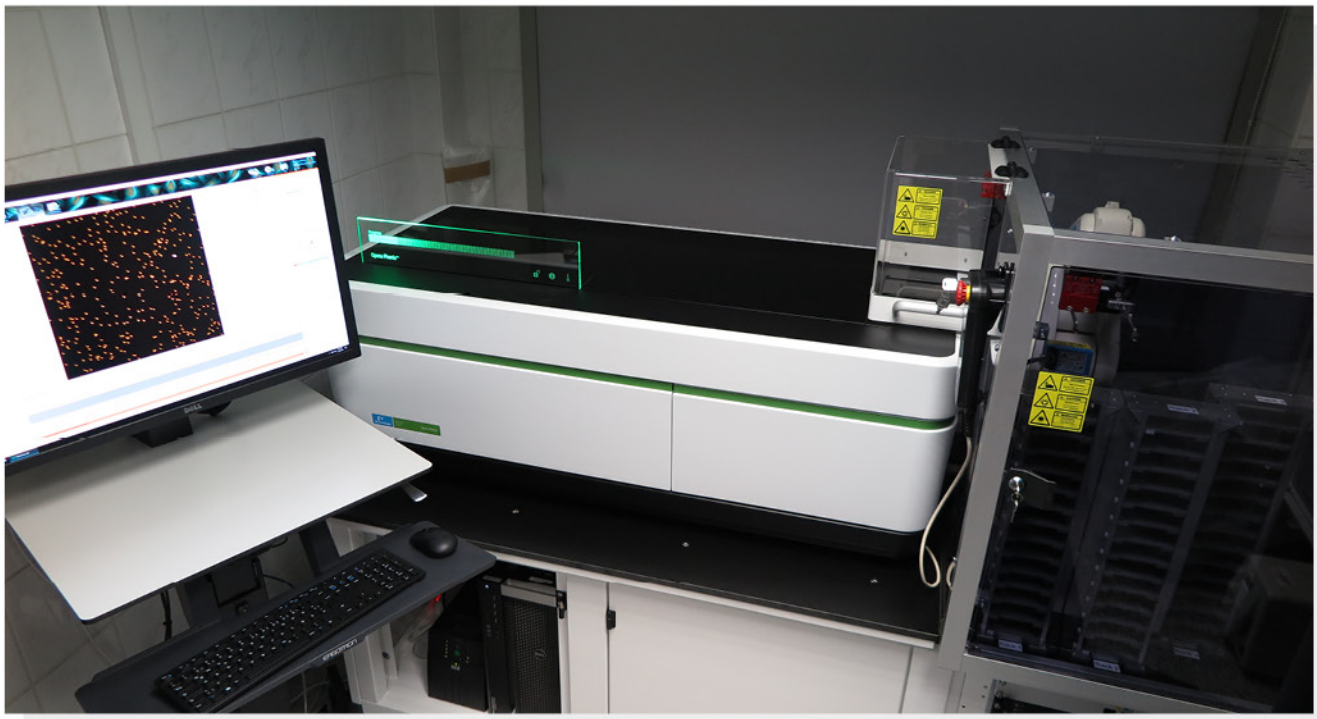
The IIMCB Core Facility was set up as a shared research resource that provides access to a broad range of cutting-edge research technology platforms that are extensively used in such diverse areas as structural biology, bioinformatics, and molecular and cell biology. The Core Facility is managed by experienced scientists who devote their time and effort to maintain the most sophisticated equipment. More than 50 pieces of equipment are grouped into several units according to leading technologies and applications.

The Macromolecule Crystallography Unit is one of the most advanced in Poland. Proteins are purified with several chromatographic FPLC systems and subjected to crystallization using two crystallization robots and ~1,000 crystallization conditions (buffers). The crystallization process is performed in a crystallization hotel at 4°C or 18°C, and progress is tracked by a CCD camera. The crystals are analyzed using an X-ray generator (Proteum Bruker) that is equipped with a CCD detector (Platinum 135) and cryostream cooler (Oxford Cryosystems series 700). This facility allows the collection of a complete set of diffraction data within a few hours.

The Biochemical and Biophysical Analysis of Proteins and Nucleic Acids Unit is equipped with analytical instruments for in-depth analyses of proteins and nucleic acids using different methods. Interactions between molecules are studied using several complementary techniques: microcalorimetry (VP-DSC and VP-ITC) and analytical ultracentrifugation AUC (Beckman Coulter ProteomeLab XL-I). We use the Anton Paar DMA 5000 M and rolling-ball viscometer Lovis 2000 M, the world's most accurate density meter, to precisely determine buffer properties. The size of the macromolecular complexes is measured by size exclusion chromatography with a multiangle light-scattering (SEC-MALS) detector and AUC. We are also equipped with a wide selection of spectrometers, including spectrophotometers, spectrofluorometers, a CD spectropolarimeter, and an FT-IR spectrometer. The list of instruments has recently been broadened by a new Biacore S200 surface plasmon resonance instrument, the most sensitive equipment of this class, which replaced the Biacore 3000.

The Mass Spectrometry of Proteins and Nucleic Acids Unit has two mass spectrometers: MALDI-TOF-TOF (ultrafleXtreem, Bruker) and LC-ESI-Ion Trap (amaZon speed ETD, Bruker). In addition to prompt standard proteomics analysis (protein identification and protein integrity assays) for internal users, which are vital for crystallography projects, we provide non-standard analyses of macromolecules other than proteins, particularly analyses of RNA samples and nucleosides. The use of MS analysis for RNA targets makes this facility a unique entity nationwide.

The Fluorescence Bioimaging Unit offers fluorescence-based imaging systems that are suited for cell biology applications. Our microscopes either work in wide-field mode or use one of several optical sectioning techniques: confocal, two-photon, lightsheet, and TIRF. The newest acquisition is Opera Phenix, a high-content screening system from Perkin-Elmer for the large-scale imaging of cells in wide-field or confocal mode (e.g., in RNAi-based microscopy screens). Other equipment includes a Zeiss LSM800 confocal microscope with a high-resolution Airyscan detector, a Zeiss LSM710 NLO dual confocal/multiphoton microscope for the live imaging of cells and tissues, an Andor Revolutions XD system for real-time spinning-disk confocal microscopy and TIRF imaging,



Opera Phenix is a spinning disk-based confocal microscope equipped with two cameras, a laser-based autofocus system and an automated system for water immersion. The microscope can scan automatically multi-well plates and slides. Moreover, the system installed at IIMCB has a robotic arm for automated plate handling.

a Zeiss Lightsheet Z.1 single-plane illumination microscope (SPIM) for the imaging of fluorescently labeled zebrafish larvae, an Olympus CellR/ ScanR imaging station for intracellular calcium measurements and the semi-high-throughput quantitative analysis of fluorescence signals, and a Nikon 80i Eclipse microscope with a scanning stage for the mosaic imaging of histochemically or fluorescently stained tissue sections. Image analysis in 2D and 3D is possible using dedicated software, such as Imaris and Harmony. Electrophysiological recordings and the imaging of cultured neurons and brain slices are performed on Zeiss Examiner.Z1. The unit also has a BD FACSAria II for cell sorting and BD FACSCalibur for the quantitative analysis of suspension cells.

FEI Tecnai T12 Transmission Electron Microscope. T12 is supported by Core Facility for conventional imaging of cells and tissue samples. In general, the system is combined with the TemCam F-Series camera and mostly used for structural biology and analysis of protein complexes both conventionally and with Cryo-EM. One of the greatest advantages of Cryo-EM relative to conventional structural biology techniques is its ability to analyze large, complex, and flexible structures, which oftentimes cannot be crystallized. Moreover, T12 microscope can be used to investigate polymers, thin films, fibers, ceramics, powders, and single crystals. The TEM is supplemented with Quorum Q150T ES, necessary for sample preparation as hydrophilization (wetting) of films and grids for TEM. The Q150T ES also allows deposition of layers of carbon on grids. As part of our Cryo-TEM workflow, we have a Vitrobot FEI, which offers fully automated cryo-fixation process (vitrification) under constant physical and mechanical conditions. This ensures high-quality cryo-fixation results and high sample preparation throughput prior to cryo-TEM observations. For conventional TEM of cells and tissue samples preparation Core Facility offers Tissue processor Leica EM TP. This is a tool designed for EM and LM resin processing under constant temperature, avoiding exposure to toxic substances. After saturation with resin, tissue and cell samples are cut on our Ultramicrotome Leica EM UC7, which enables the easy preparation of semi- and ultrathin sections and perfect, smooth surfaces of biological and industrial samples for TEM, SEM, AFM, and LM examination.

The Next Generation Sequencing (NGS) Unit is equipped with an Illumina NextSeq 500 sequencer and provides instrumentation for complete sample preparation for sequencing. This includes systems for precise DNA/RNA/chromatin shearing and size selection (Covaris M220, BioRuptor Pico, BluePippin), and systems for nucleic acid quality and quantity measurements (TapeStation 2200, NanoDrop 3300, and Quantus). Moreover NGS Unit offers platform for data analysis and storage. The NGS system is already extensively used for the genomic, transcriptomic, and genome methylation sequencing of higher eukaryotes. The purchase of the NGS unit was supported by a Polish Ministry of Science and Higher Education equipment grant for the scientific consortium of IIMCB and Museum and Institute of Zoology, Polish Academy of Sciences. We also operate one MinION unit (third-generation sequencing) in the Oxford Nanopore MinION access program.

The Core Facility provides flexible assistance with methodological principles, experimental design, initial training, procedures that are needed for specific experiments, data analysis, and final interpretation, serving as a link between scientists and state-of-the-art technology. The Core Facility is also available to scientists from other institutions. IIMCB emphasizes cooperation with rapidly developing biotech companies in Poland. Within the framework of bilateral agreements, IIMCB laboratories collaborated with biotech companies, such as Adamed, Celon Pharma, Fermentas, BioVectis, Glia, Polfa, OncoArendi Therapeutics, and Helix Immuno-Oncology.

The biophysical part of the Core Facility is one of the founding members of the Association of Resources for Biophysical Research in Europe (ARBRE) and Core Technologies for Life Sciences (CTLS) network. We represent Poland on the Management Committee of the COST Action "MOBIEU" ("Between Atom and Cell: Integrating Molecular Biophysics Approaches for Biology and Healthcare"). In 2018 (March 19-21), we organized an annual plenary meeting of this action: "Talking molecules: The networks that shape the living world."

Zebrafish Core Facility

The Zebrafish Core Facility (ZCF) has existed since 2012. It is a licensed breeding and research facility (District Veterinary Inspectorate in Warsaw registry no. PL14656251; Ministry of Science and Higher Education record no. 064 and 051). The facility was established to introduce a new vertebrate model to research that is conducted at IIMCB. Moreover, **as a first in Poland, the ZCF joined the prestigious European Society for Fish Models in Biology and Medicine (EuFishBioMed) and is registered in the Zebrafish Model Organism Database (ZFIN).**

Zebrafish is a small (3-5 cm) tropical freshwater fish. Thanks to its high genetic similarity to humans, very short reproduction cycle and generation of transparent embryos, zebrafish is an excellent model for biomedical research. Moreover, the access to experimental manipulations, extensive collection of mutant/transgenic animals, and low maintenance cost make zebrafish an attractive alternative to mammalian *in vivo* models and can be used to implement the "3R" principles (reduction, replacement, and refinement). In 2013, approximately 6,000 fish (30 lines) were kept in the ZCF in 300 tanks (50 tanks in quarantine and 250 tanks in the main system). **Currently, our zebrafish collection consists of more than 19 000 fish, including four wildtype lines and more than 120 genetically modified lines** (see examples in Table 1). Numerous zebrafish mutants were generated using methods that are based on engineered endonucleases, such as transcription activator-like effector nucleases (TALENs) and the bacterial type II clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system.

Among the ZCF collection are animals that express modified genes that are involved in the mTOR signaling pathway, mitochondrial processes, heart development, and neurodegenerative disorders. The ZCF and research groups use zebrafish in innovative projects on genetics, developmental biology, and molecular mechanisms of human diseases. Currently, seven research groups from IIMCB use zebrafish and equipment resources of the ZCF. In 2018, the ZCF also served **external users**, including research groups from the Centre of New Technologies at the University of Warsaw, Medical University of Warsaw, Warsaw University of Life Sciences, Nencki Institute of Experimental Biology, Medical University of Lublin, University of Warmia and Mazury in Olsztyn, University of Wrocław, and Institute of Industrial Organic Chemistry in Pszczyna. Additionally, because of our international reputation and scientific collaborations, every year we export fish lines to European and American scientific institutes, such as Manchester (UK), New York (USA), and Bad Nauheim (Germany).

Maintaining such a large number of fish would not be possible without a suitable infrastructure. **Our fish are currently housed in 1 210 tanks (eight independent, automated aquatic systems)** that are manufactured by Techniplast. Moreover, the ZCF is equipped with embryo incubators, stereomicroscopes connected with microinjection systems, a PCR thermocycler and fluoromicroscope. Additionally, ZCF users have at their disposal an isolated room dedicated to behavioral testing, that is equipped with two automated systems for observations and the tracking of larval and adult zebrafish. The ZCF also performs sperm freezing and *in vitro* fertilization to guarantee the preservation of zebrafish genetic lines. **The zebrafish diagnostic and health service is conducted by an IIMCB veterinarian (an expert in the aquatic field and tropical fish diseases) in cooperation with an external zebrafish diagnostic laboratory, which allows us to constantly monitor the health status of the fish colony and maintain the highest standards of animal welfare.**

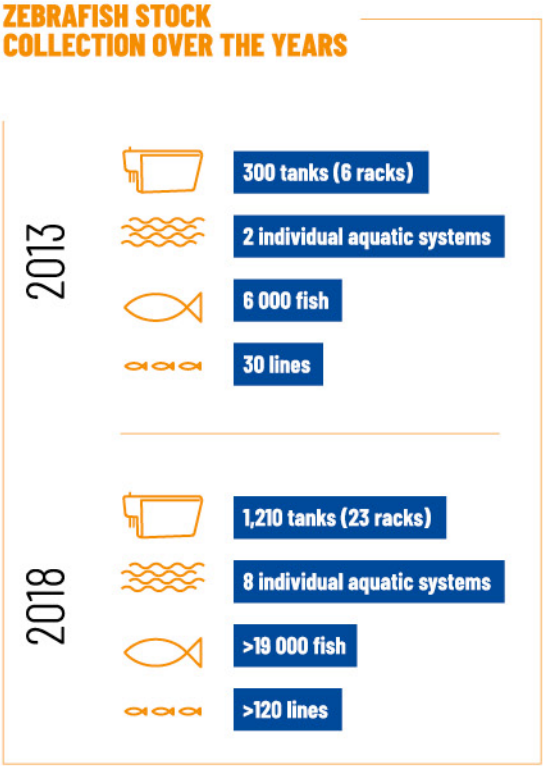
Scientists who use zebrafish for research purposes are obligated by law (Act of 15 January 2015 on the Protection of Animals Used for Scientific or Educational Purposes) to possess appropriate qualifications to work with an animal model. All of the research and breeding activities at the ZCF are performed in compliance with fundamental ethical principles (Act of 15 January 2015 and European/International guidelines on animal welfare, including Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes and the instructions of the Federation of European Laboratory Animal Science Associations [FELASA]).

The ZCF team consists of eight members, including head of the facility, veterinarian, animal caretakers, and technician. ZCF personnel provide training courses to new users of the facility, including practical elements of handling, husbandry, breeding, fin clipping, microinjections, and behavioral testing. The ZCF is open for zebrafish users 5 days per week: Monday to Thursday from 8 AM to 5 PM and Friday from 8 AM to 4 PM.

Table. 1 Example of zebrafish lines currently kept in the ZCF stock (note that the usage of some lines is limited by MTAs):

WILDTYPE LINES	MUTANT LINES				TRANSGENIC LINES
Name	Name	Affected genomic region	Allele	Molecular change	Name
AB	albino	slc45a2	unknown	unknown	Tg(ath5:gap43GFP)
TL	casper	(roy x nacre)	unknown	unknown	Tg(brn3c:mGFP)
ABTL	dackel	ext2	to273b	point mutation	Tg(cmlc2:GFP)
TU	fmr1	fmr1	hu2787	point mutation	Tg(cmlc2:mRFP)
	gata5	gata5	tm236a	point mutation	Tg(CMV:GFP-map1lc3b)
	gba1	gba1	sh391	small deletion	Tg(fabp10a:dsRed)
	hand2	hand2	Hanc99	insertion	Tg(fli:eGFP)
	nacre	mitfa	unknown	unknown	Tg(flt1BAC:YFP)
	ogr	tbx5	Hstm21	unknown	Tg(gata1:dsRed)
	pink1	pink1	sh397	point mutation	Tg(gata1:dsRed;globin:GFP)
	pinscher	slc35b2	to216z	point mutation	Tg(-14.8gata4:GFP)
	CR2:stim2b	stim2b		insertion	Tg(hand2:GFP)
	tbx5	tbx5	Hstm21	point mutation	Tg(kdr-l:mCherry-CAAX)
	tet1	tet1	g.74453	deletion	Tg(mnx1:TagRFP-T)
	tet2	tet2	g.23316	deletion	Tg(myl7:eGFP)
	tet3	tet3	g.52494	deletion	Tg(nkx2.5:eGFP)
	tsc2	tsc2	vu242	point mutation	Tg(ptf1a:GFP)
	mtor(ztor)	mtor(ztor)	xu015	transgenic insertion	Tg(vas:eGFP)

ZEBRAFISH STOCK COLLECTION OVER THE YEARS



Zebrafish Core Facility at IIMCB

ProBiostructures

Co-founder, Chief Scientific Officer
Marcin Nowotny, PhD, DSc Habil

Co-founder, Chief Executive Officer
Paweł Kustosz, MSc

Business Development Support
Rafał Igielski, MSc

Researchers
Malwina Hyjek, PhD
Agnieszka Napiórkowska, MSc

Technician
Iwona Ptasiewicz (part-time)

PRO BIOSTRUCTURES
IIMCB STRUCTURAL BIOLOGY CENTER

SERVICES

ProBiostructures provides services and consultancy in the field of structural biology with an emphasis on supporting drug discovery projects. The venture comprises a complete range of X-ray crystallography and cryo-electron microscopy research, called "gene to structure", that is enriched with the biophysical and biochemical characterization of target-ligand interactions.

MOTTO

Our team is made for your difficult challenges

EXPERIENCE

ProBiostructures cooperates closely with leading pharmaceutical companies in central Europe (e.g., Selvita, Celon Pharma, OncoArendi Therapeutics, Adamed) and with UbiQ Bio in the Netherlands and IONIS Pharmaceuticals in the United States. Structural biology, biophysics and biochemistry services have supported drug discovery efforts for such diseases as cancer, asthma, and depression. ProBiostructures solved a crystal structure of OncoArendi's OATD-01 compound with a target protein. The compound is undergoing clinical trials and in the case of positive results will be the first sarcoidosis drug on the market, with a new mechanism of action (first in class). In addition to profitable commercial projects, ProBiostructures also scientifically cooperates with foreign companies from the biotechnology and pharmaceutical sectors. Such collaborations are an investment in promoting the laboratory by presenting scientific potential, expertise in R&D projects, and a flexible approach to cooperation with industry. The aim of cooperation with IONIS Pharmaceuticals, the leader in RNA-targeted drug discovery, is to develop a new service which supports nucleic acid-based therapeutics discovery. The purpose of the collaboration with the UbiQ Bio is to publish in a high-impact journal to present a new cryo-EM service. Both agreements lead to long-term international trade partnerships.

X-RAY CRYSTALLOGRAPHY - SERVICE

X-Ray crystallography is a well-established and routine method the team has applied in numerous R&D and scientific projects. A remarkable advantage is unique expertise in the crystallization of protein-nucleic acid complexes. This expertise can be used to understand the mode of action of nucleic acid-based therapeutic agents and to understand the mechanism of nucleic acid enzymes to devise better strategies of their inhibition. One good example of therapeutically important but underexplored nucleic acid enzymes are proteins that are involved in DNA repair.

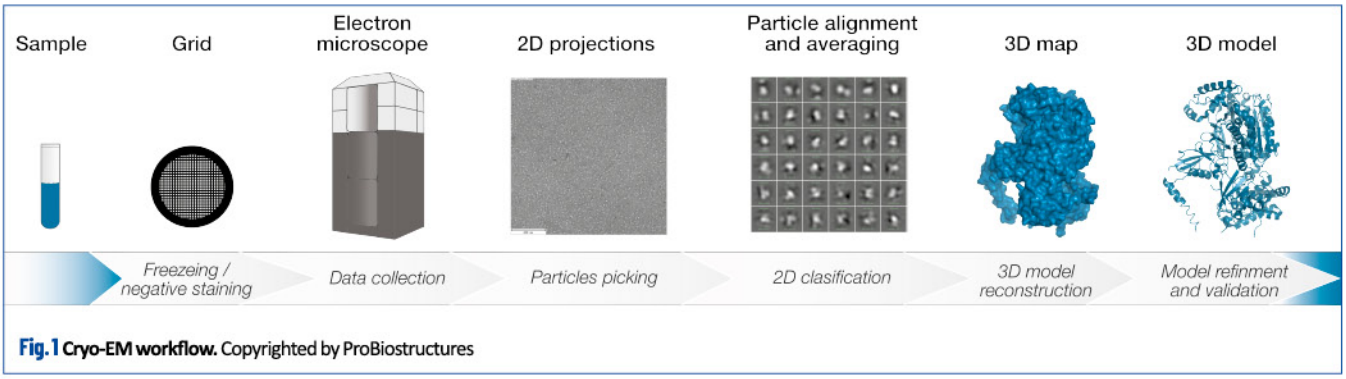


Fig. 1 Cryo-EM workflow. Copyrighted by ProBiostructures

CRYO-EM - SERVICE

In 2017, the Nobel Prize in Chemistry was awarded to Jacques Dubochet, Joachim Frank, and Richard Henderson "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution." This novel approach enables the determination of high-resolution structures of proteins under near native condition at close to atomic resolution and complements existing atomic-resolution approaches, such as X-ray crystallography. Recent publications show that cryo-EM can be used to investigate a broad spectrum of drug-target interactions with routine resolution of ~4 Å, possibly up to 2 Å. Cryo-EM enables the analysis of proteins or protein complexes with a molecular weight ≥ 150 kDa (e.g., antibodies and membrane proteins) that are otherwise difficult or impossible to analyze using other structural biology methods.

EXPERTISE

The success of the company derives from the highest level of expertise in science, advanced skills, and the excellent quality of services that are rendered. It offers the extensive experience of top scientists in biomedicine research with significant scientific output (publications in such journals as Cell, Molecular Cell, and Nature Structural and Molecular Biology) and recipients of prestigious research grants. The laboratory also promotes its operations through biotechnology and pharmaceutical industry conferences and events, such as BioEurope, BioEurope Spring, BioJapan, BioFIT, and Life Sciences Baltics.

CUSTOMIZATION

The modular service packages meet the needs of business clients in state-of-the art, flexible, and custom-made projects and protect the Intellectual Property rights of the clients at every step. With ongoing projects, the project manager keeps in touch with clients on progress throughout the project to ensure maximum success.

DATA PROTECTION

For secure data exchange with our partners, we are using Office 365 Cloud Services–OneDrive for Business and SharePoint Online. If the company has a different system, then we are ready to open an independent sub-account for it or use another system.

STARTING NEW PROJECTS AND RISK SHARING

Each project starts with a feasibility assessment. Afterward, preliminary experiments are conducted at a price of the operational costs (risk sharing). When ProBiostructures delivers satisfactory project results, the final price consists entirely of a success fee.

PROBIOSTRUCTURES OFFERS A FLEXIBLE APPROACH TO THE MOST ADVANCED RESEARCH IN

- Preparation of expression constructs.
- Recombinant protein production in bacteria, yeast, LEXSY, baculovirus-insect cells, and mammalian cells.
- X-ray crystallography of protein or protein-ligand complexes (structure-based drug design, hit-to-lead, and structure-based lead optimization).
- Single-particle cryo-electron microscopy (cryo-EM) with the goal of determining high-resolution structures of macromolecules with a molecular weight ≥ 150 kDa.
- Biophysical/biochemical characterization of target-ligand interactions (e.g., Biacore SPR, ITC, fluorescence anisotropy), assay design, and optimization.

PROJECTS

IONIS Pharmaceuticals
Solving protein-nucleic acid drug structures and joint patent development

UbiQ Bio
Solving protein-inhibitor structures and scientific cooperation using cryo-EM

Adamed Pharma
Solving protein-inhibitor structures (four structures were solved, the results of which will be published soon)

Celon Pharma
Protein production and its biophysical characterization: prestigious InnoNeuroPharm NCBR grant

OncoArendi Therapeutics
Solving protein-inhibitor structures (13 structures were solved, the results of which will be published soon).

WHAT A CLIENT SAYS ABOUT PROBIOSTRUCTURES

High quality of research, unique skills and experience and flexibility keep OncoArendi Therapeutics expanding the collaboration with ProBiostructures within new drug discovery projects.

Karolina Dzwonek, PhD - VP Biologics - OncoArendi Therapeutics

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Biotech Innovations Ltd

Chief Executive Officer
Iwona Cymerman, PhD

MISSION

Biotech Innovations Ltd is a special-purpose vehicle that is funded by IIMCB. It is the successor to the "Bio&Technology Innovations Platform" Technology Transfer Office. Biotech Innovations is committed to turning scientific progress into marketable products and technologies and returning income to inventors and IIMCB to support further research. The company manages a portfolio of patents and patent applications and supports the development of the most commercially advanced projects in the economic environment.

ACTIVITIES

Our work begins with disclosures of inventions of IIMCB scientists. We review new inventions to learn about their applicability and commercial potential. We then define value propositions for industry licensees. Together with the inventors, we look for companies that might be interested in the invention. We also support scientists who wish to stay actively involved in the further development of their invention and seek to set up a spin-off company.

To raise awareness among academics about intellectual property rights and possibilities of transferring R&D results to industry, we regularly hold seminars on "IP Policy for Management and Use of Intellectual Property of IIMCB."

To encourage IIMCB scientists to undertake steps toward validating the applicability of their discoveries in industry, we also designed and launched the internal grant program "Commercialization Quest." In 2018, the project of Dr. Łukasz Majewski, "Looking for novel potential therapeutic targets in epilepsy," was funded to boost commerciality of the project.

Biotech Innovations Ltd ✉ contact@biotech-innovations.com 🌐 biotech-innovations.com

FACTS & FIGURES

Publications in 2018

LIST OF PAPERS WITH IIMCB-AFFILIATED MAIN AUTHORS (FIRST AND/OR CORRESPONDING)

No	Authors	Title	Journal	5 Year IF	Journal Category	Journal Rank in Category/ Total Journals in Category	Quartile in Category
1	**Razew M**, Warkocki Z, Taube M, Kolondra A, **Czarnocki-Cieciura M, Nowak E**, Labedzka-Dmoch K, Kawinska A, Piatkowski J, Golik P, Kozak M, Dziembowski A, **Nowotny M.**	Structural analysis of mtEXO mitochondrial RNA degradosome reveals tight coupling of nuclease and helicase components.	Nat Commun, 2018; 9(1):97	13.691	MULTIDISCIPLINARY SCIENCES	3 of 64	1
2	**Topf U, Suppanz I, Samluk L, Wrobel L**, Böser A, **Sakowska P**, Knapp B, **Pietrzyk MK, Chacinska A**, Warscheid B.	Quantitative proteomics identifies redox switches for global translation modulation by mitochondrially produced reactive oxygen species.	Nat Commun, 2018; 9(1):324	13.691	MULTIDISCIPLINARY SCIENCES	3 of 64	1
3	**Boccaletto P, Machnicka MA, Purta E, Piatkowski P, Baginski B, Wirecki TK**, de Crécy-Lagard V, Ross R, Limbach PA, Kotter A, Helm M, **Bujnicki JM.**	MODOMICS: a database of RNA modification pathways. 2017 update.	Nucleic Acids Res, 2018; 46(D1):D303-D307	10.235	BIOCHEMISTRY & MOLECULAR BIOLOGY	10 of 293	1
4	**Boccaletto P, Magnus M, Almeida C, Zyla A, Astha, Piuta R, Baginski B, Jankowska E, Dunin-Horkawicz S, Wirecki T, Boniecki M, Stefaniak F, Bujnicki JM.**	RNArchitecture: a database and a classification system of RNA families, with a focus on structural information.	Nucleic Acids Res, 2018; 46(D1):D202-D205	10.235	BIOCHEMISTRY & MOLECULAR BIOLOGY	10 of 293	1
5	**Czapinska H, Kowalska M,** Zagorskaite E, Manakova E, **Slyvka A**, Xu SY, Siksnys V, Sasnauskas G, **Bochtler M.**	Activity and structure of EcoKMcrA.	Nucleic Acids Res, 2018; 46(18):9829-41	10.235	BIOCHEMISTRY & MOLECULAR BIOLOGY	10 of 293	1
6	**Kisiala M**, Copelas A, **Czapinska H**, Xu S, **Bochtler M.**	Crystal structure of the modification-dependent SRA-HNH endonuclease Tagl	Nucleic Acids Res, 2018; 46(19):10489-503	10.235	BIOCHEMISTRY & MOLECULAR BIOLOGY	10 of 293	1
7	Wawrzynow B, **Zylicz A, Zylicz M.**	Chaperoning the guardian of the genome. The two-faced role of molecular chaperones in p53 tumor suppressor action.	Biochim Biophys Acta-Reviews on Cancer, 2018; 1869(2):161-174	8.901	BIOCHEMISTRY & MOLECULAR BIOLOGY	24 of 293	1
8	**Kowalski L, Bragoszewski P**, Khmelinskii A, **Glow E**, Knop M, **Chacinska A.**	Determinants of the cytosolic turnover of mitochondrial intermembrane space proteins.	BMC Biol, 2018; 16(1):66	7.436	BIOLOGY	6 of 85	1
9	**Toczydlowska-Socha D, Zielinska MM, Kurkowska M, Astha, Almeida CF, Stefaniak F, Purta E, Bujnicki JM.**	Human RNA cap1 methyltransferase CMTr1 cooperates with RNA helicase DHX15 to modify RNAs with highly structured 5' termini.	Philos Trans R Soc Lond B Biol Sci, 2018; 373(1762) pii: 20180161	7.192	BIOLOGY	7 of 85	1
10	**Sokol AM**, Uszczynska-Ratajczak B, Collins MM, **Bazala M, Topf U**, Lundegaard PR, **Sugunan S**, Guenther S, Kuenne C, Graumann J, Chan SSL, Stainier DYR, **Chacinska A.**	Loss of the Mia40a oxidoreductase leads to hepato-pancreatic insufficiency in zebrafish.	PLOS Genet, 2018; 14(11):e1007743	6.685	GENETICS & HEREDITY	22 of 171	1
11	**Szymanska E, Budick-Harmelin N, Miaczynska M.**	Endosomal „sort" of signaling control: The role of ESCRT machinery in regulation of receptor-mediated signaling pathways.	Semin Cell Dev Biol. 2018; 74:11-20	6.273	CELL BIOLOGY	38 of 190	1
12	**Winata CL, Łapiński M, Pryszcz** L, Vaz C, Bin Ismail MH, Nama S, Hajan HS, Lee SGP, **Korzh V**, Sampath P, Tanavde V, Mathavan S.	Cytoplasmic polyadenylation-mediated translational control of maternal mRNAs directs maternal to zygotic transition.	Development, 2018; 145(1) pii: dev159566	6.134	DEVELOPMENTAL BIOLOGY	5 of 42	1
13	**Korzh V.**	Development of brain ventricular system.	Cell Mol Life Sci, 2018; 75(3):375-383	6.134	BIOCHEMISTRY & MOLECULAR BIOLOGY	34 of 293	1

14	**Pluta R**, Espinosa M.	Antisense and yet sensitive: Copy number control of rolling circle-replicating plasmids by small RNAs.	Wiley Interdiscip Rev RNA, 2018; 9(6):e1500	6.004	CELL BIOLOGY	40 of 190	1
15	**Stroynowska-Czerwinska A, Piasecka A, Bochtler M.**	Specificity of MLL1 and TET3 CXXC domains towards naturally occurring cytosine modifications.	Biochim Biophys Acta-Gene Regul Mech, 2018; 1861(12):1093-1101	5.547	BIOCHEMISTRY & MOLECULAR BIOLOGY	48 of 293	1
16	**Koscielny A, Malik AR, Liszewska E, Zmorzynska J, Tempes A, Tarkowski B, Jaworski J.**	Adaptor Complex 2 Controls Dendrite Morphology via mTOR-Dependent Expression of GluA2.	Mol Neurobiol, 2018; 55(2):1590-1606	5.136	NEUROSCIENCES	44 of 261	1
17	**Banach-Orlowska M, Jastrzębski K, Cendrowski J, Maksymowicz M, Wojciechowska K,** Korostyński M, Moreau D, Gruenberg J, **Miaczynska M.**	The topology of lymphotoxin β receptor accumulated upon endolysosomal dysfunction dictates the NF-κB signaling outcome.	J Cell Sci, 2018; 131(22) pii: jcs.218883	5.094	CELL BIOLOGY	62 of 190	2
18	**Czeredys M,** Vigont VA, Boeva VA, Mikoshiba K, Kaznacheyeva EV, **Kuznicki J.**	Huntingtin-Associated Protein 1A Regulates Store-Operated Calcium Entry in Medium Spiny Neurons From Transgenic YAC128 Mice, a Model of Huntington's Disease.	Front Cell Neurosci, 2018; 12:381	4.915	NEUROSCIENCES	62 of 261	1
19	**Folk IP, Tuszynska I, Feder M, Purta E, Stefaniak F, Bujnicki JM.**	Novel inhibitors of the rRNA ErmC' methyltransferase to block resistance to macrolides, lincosamides, streptogramine B antibiotics.	Eur J Med Chem, 2018; 146:60-67	4.527	CHEMISTRY, MEDICINAL	4 of 59	1
20	Balaji V, **Pokrzywa W,** Hoppe T.	Ubiquitylation Pathways in Insulin Signaling and Organismal Homeostasis.	Bioessays, 2018; 40(5):e1700223	4.391	BIOCHEMISTRY & MOLECULAR BIOLOGY	62 of 293	1
21	**Figiel M,** Krepl M, Park S, Poznański J, **Skowronek K,** Gołąb A, Ha T, Šponer J, **Nowotny M.**	Mechanism of polypurine tract primer generation by HIV-1 reverse transcriptase.	J Biol Chem, 2018; 293(1):191-202	4.254	BIOCHEMISTRY & MOLECULAR BIOLOGY	75 of 293	2
22	Piasecka A, **Czapinska H,** Vielberg MT, **Szczepanowski RH,** Kiefersauer R, Reed S, Groll M, **Bochtler M.**	The Y. bercovieri Anbu crystal structure sheds light on the evolution of highly (pseudo) symmetric multimers.	J Mol Biol, 2018; 430(5):611-627	4.242	BIOCHEMISTRY & MOLECULAR BIOLOGY	54 of 293	1
23	**Winata CL, Korzh V.**	The translational regulation of maternal mRNAs in time and space.	FEBS Lett, 2018; 592(17):3007-23	3.373	BIOCHEMISTRY & MOLECULAR BIOLOGY	140 of 293	2
24	**Pawlak M, Niesclerowicz K, Winata CL.**	Decoding the Heart through Next Generation Sequencing Approaches.	Genes (Basel), 2018; 9(6) pii: E289	3.286	GENETICS & HEREDITY	68 of 171	2
25	**Nithin C, Ghosh P, Bujnicki JM.**	Bioinformatics Tools and Benchmarks for Computational Docking and 3D Structure Prediction of RNA-Protein Complexes.	Genes (Basel), 2018; 9(9):E432	3.286	GENETICS & HEREDITY	68 of 171	2
26	**Wegierski T, Kuznicki J.**	Neuronal calcium signaling via store-operated channels in health and disease.	Cell Calcium, 2018; 74:102-111	3.215	CELL BIOLOGY	81 of 190	2
27	**Fernandes H, Czapinska H, Grudziaz K, Bujnicki JM, Nowacka M.**	Crystal structure of human Acinus RNA recognition motif domain.	PeerJ, 2018; 6:e5163	2.469	MULTIDISCIPLINARY SCIENCES	19 of 64	2
28	**Hareza A,** Bakun M, Świderska B, Dudkiewicz M, **Koscielny A, Bajur A, Jaworski J,** Dadlez M, Pawłowski K.	Phosphoproteomic insights into processes influenced by the kinase-like protein DIA1/C3orf58.	PeerJ, 2018; 6:e4599	2.469	MULTIDISCIPLINARY SCIENCES	19 of 64	2
29	**Szybalska A,** Broczek K, Puzianowska-Kuznicka M, **Slusarczyk P,** Chudek J, Skalska A, **Mossakowska M.**	Self-rated health and its association with all-cause mortality of older adults in Poland: The PolSenior project.	Arch Gerontol Geriatr, 2018; 79:13-20	2.449	GERIATRICS & GERONTOLOGY	34 of 53	3
30	**Pruszko M,** Milano E, **Zylicz A, Zylicz M,** Blandino G, Fontemaggi G.	Zebrafish as experimental model to establish the contribution of mutant p53 and ID4 to breast cancer angiogenesis in vivo.	J Thorac Dis, 2018; 10(3):E231-E233	2.015	RESPIRATORY SYSTEM	47 of 60	4
31	**Dodzian J,** Kean S, Seidel J, Valenzano DR.	A Protocol for Laboratory Housing of Turquoise Killifish (Nothobranchius furzeri).	J Vis Exp, 2018; (134)	1.677	MULTIDISCIPLINARY SCIENCES	31 of 64	2
32	**Jaworski J,** Kalita K, Knapska E.	c-Fos and neuronal plasticity: the aftermath of Kaczmarek's theory.	Acta Neurobiol Exp, 2018;78(4):287-296	1.631	NEUROSCIENCES	230 of 261	4

33	**Szybalska A**, Broczek K, **Siusarczyk P**, Kozdron, Chudek J, Puzianowska-Kuznicka M, Kostka T, Skalska A, **Mossakowska M.**	Utilization of medical rehabilitation services among older Poles: results of the PolSenior study.	Eur Geriatr Med, 2018; 9(5):669-677	1.139	GERIATRICS & GERONTOLOGY	45 of 53	4
34	**Korzh V**, Kondrychyn I, **Winata C.**	The Zebrafish as a New Model System for Experimental Biology.	Cytol Genet, 2018; 52(6):406-415	0.343	GENETICS & HEREDITY	168 of 171	4
35	**Budick-Harmelin N, Miaczynska M.**	Integration of the Endocytic System into the Network of Cellular Functions.	Book Series: Prog Mol Subcell Biol, 2018; 57:39-63	-	-	-	-
36	**Liszewska E, Jaworski J.**	Neural Stem Cell Dysfunction in Human Brain Disorders.	Book Series: Results Probl Cell Differ, 2018; 66:283-305	-	-	-	-
37	**Szybalska A**, Broczek K, **Ślusarczyk P**, Kozdroń E, Błędowski P, Chudek J, **Mossakowska M.**	The utilization of health resort treatment services by older people in Poland – results of the PolSenior study.	Gerontologia Polska, 2018; 26:7-13	-	-	-	-
38	**Winata CL, Korzh V.**	Zebrafish Zic Genes Mediate Developmental Signaling.	Book Series: Adv Exp Med Biol, 2018; 1046:157-177	-	-	-	-

LIST OF PAPERS WITHOUT IIMCB-AFFILIATED MAIN AUTHORS (FIRST AND/OR CORRESPONDING)

No	Authors	Title	Journal	5 Year IF	Journal Category	Journal Rank in Category / Total Journals in Category	Quartile in Category
1	Lim R, **Potente M.**	Top-NOTCH Regulation of Cardiac Metabolism.	Circulation, 2018; 137(24):2609-12	17.902	CARDIAC & CARDIOVASCULAR SYSTEMS	2 of 128	1
2	Kumari P, Aeschimann F, Gaidatzis D, Keusch JJ, **Ghosh P**, Neagu A, Pachulska-Wieczorek K, **Bujnicki JM**, Gut H, Großhans H, Ciosk R.	Evolutionary plasticity of the NHL domain underlies distinct solutions to RNA recognition.	Nat Commun, 2018; 9(1):1549	13.691	MULTIDISCIPLINARY SCIENCES	3 of 64	1
3	Koyuncu S, Saez I, Lee HJ, Gutierrez-Garcia R, **Pokrzywa W**, Fatima A, Hoppe T, Vilchez D.	The ubiquitin ligase UBR5 suppresses proteostasis collapse in pluripotent stem cells from Huntington's disease patients.	Nat Commun, 2018; 9(1):2886	13.691	MULTIDISCIPLINARY SCIENCES	3 of 64	1
4	Wojtczak BA, Sikorski PJ, Fac-Dabrowska K, Nowicka A, Warminski M, Kubacka D, **Nowak E, Nowotny M**, Kowalska J, Jemielity J.	5'-Phosphorothiolate Dinucleotide Cap Analogues: Reagents for Messenger RNA Modification and Potent Small-Molecular Inhibitors of Decapping Enzymes.	J Am Chem Soc, 2018; 140(18):5987-99	13.613	CHEMISTRY, MULTIDISCIPLINARY	8 of 171	1
5	Voigt C, Dobrychlop M, Kruse E, Czerwoniec A, Kasprzak JM, Bytner P, Campo CD, Leeder WM, **Bujnicki JM**, Göringer HU.	The OB-fold proteins of the Trypanosoma brucei editosome execute RNA-chaperone activity.	Nucleic Acids Res, 2018; 46(19):10353-67	10.235	BIOCHEMISTRY & MOLECULAR BIOLOGY	10 of 293	1
6	NCD Risk Factor Collaboration (NCD-RisC) within **Mossakowska M, Siusarczyk P.**	Contributions of mean and shape of blood pressure distribution to worldwide trends and variations in raised blood pressure: a pooled analysis of 1018 population-based measurement studies with 88.6 million participants.	Int J Epidemiol, 2018; 47(3):872–883i	10.177	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	5 of 181	1
7	Bennabi I, Quéguiner I, **Kolano A**, Boudier T, Mailly P, Verlhac MH, Terret ME.	Shifting meiotic to mitotic spindle assembly in oocytes disrupts chromosome alignment.	EMBO Rep, 2018; 19(2):368-381	9.127	BIOCHEMISTRY & MOLECULAR BIOLOGY	20 of 293	1
8	Brendel M, **Jaworska A**, Overhoff F, Blume T, Probst F, Gildehaus FJ, Bartenstein P, Haass C, Bohrmann B, Herms J, Willem M, Rominger A.	Efficacy of chronic BACE1 inhibition in PS2APP mice depends on the regional Aβ deposition rate and plaque burden at treatment initiation.	Theranostics, 2018; 8(18):4957-68	9.009	MEDICINE, RESEARCH & EXPERIMENTAL	8 of 133	1
9	Jurcik A, Bednar D, Byska J, Marques SM, Furmanova K, Daniel L, Kokkonen P, **Brezovsky J**, Strnad O, Stourac J, Pavelka A, Manak M, Damborsky J, Kozlikova B.	CAVER Analyst 2.0: Analysis and Visualization of Channels and Tunnels in Protein Structures and Molecular Dynamics Trajectories.	Bioinformatics, 2018; 34(20):3586-3588	8.561	BIOCHEMICAL RESEARCH METHODS	6 of 79	1
10	Neto F, Klaus-Bergmann A, Ong YT, Alt S, Vion AC, Szymborska A, Carvalho JR, Hollfinger I, Bartels-Klein E, Franco CA, **Potente M**, Gerhardt H.	YAP and TAZ regulate adherens junction dynamics and endothelial cell distribution during vascular development.	Elife, 2018 Feb 5;7. pii: e31037	8.508	BIOLOGY	4 of 85	1

11	Donzelli S, Milano E, **Pruszko M**, Sacconi A, Masciarelli S, Iosue I, Meiucci E, Gallo E, Terrenato I, Mottolese M, **Zylicz M**, **Zylicz A**, Fazi F, Blandino G, Fontemaggi G.	Expression of ID4 protein in breast cancer cells induces reprogramming of tumour-associated macrophages.	Breast Cancer Res, 2018; 20(1):59	6.272	ONCOLOGY	35 of 223	1
12	Walerych D, Pruszko M, **Zyla L**, Wezyk M, Gaweda-Walerych K, **Zylicz A**.	Wild-type p53 oligomerizes more efficiently than p53 hot-spot mutants and overcomes mutant p53 gain-of-function via a „ dominant-positive" mechanism.	Oncotarget, 2018; 9(62):32063-80	5.312	ONCOLOGY	44 of 217	1
13	Jantsch MF, Quattrone A, O'Connell M, Helm M, Frye M, Macias-Gonzales M, Ohman M, **Ameres** S, Willems L, Fuks F, Oulas A, Vanacova S, Nielsen H, Bousquet-Antonelli C, Motorin Y, Roignant JY, Balatsos N, Dinnyes A, Baranov P, Kelly V, Lamm A, Rechavi G, Pelizzola M, Liepins J, Holodnuka Kholodnyuk I, Zammit V, Ayers D, Drablos F, Dahl JA, **Bujnicki J**, Jeronimo C, Almeida R, Neagu M, Costache M, Bankovic J, Banovic B, Kyselovic J, Valor LM, Seibert S, Pir P, Demircan T, Cowling V, **Schäfer M**, Rossmanith W, Lafontaine D, David A, Carre C, Lyko F, Schaffrath R, Schwartz S, Verdel A, Klungland A, Purta E, Timotijevic G, Cardona F, Davalos A, Baliana E, O Carroll D, Ule J, Fray R.	Positioning Europe for the EPITRANSCRIPTOMICS challenge.	RNA Biol, 2018; 15(6):829-831	5.269	BIOCHEMISTRY & MOLECULAR BIOLOGY	47 of 293	1
14	Herz K, Becker A, Shi C, Ema M, Takahashi S, **Potente M**, Hesse M, Fleischmann BK, Wenzel D.	Visualization of endothelial cell cycle dynamics in mouse using the Flt-1/eGFP-anillin system.	Angiogenesis, 2018; 21(2):349-361	4.921	PERIPHERAL VASCULAR DISEASE	10 of 65	1
15	Saus E, Willis JR, **Pryszcz LP**, Hafez A, Llorens C, Himmelbauer H, Gabaldón T.	nextPARS: parallel probing of RNA structures in Illumina.	RNA, 2018; 24(4):609-619	4.874	BIOCHEMISTRY & MOLECULAR BIOLOGY	60 of 293	1
16	Hadar A, Milanesi E, Walczak M, Puzianowska-Kuźnicka M, **Kuźnicki J**, Squassina A, Niola P, Chillotti C, Attems J, Gozes I, Gurwitz D.	SIRT1, miR-132 and miR-212 link human longevity to Alzheimer's Disease.	Sci Rep, 2018; 8(1):8465	4.609	MULTIDISCIPLINARY SCIENCES	12 of 64	1
17	Sulicka J, Pac A, Puzianowska-Kuźnicka M, Zdrojewski T, Chudek J, Tobiasz-Adamczyk B, **Mossakowska M**, Skalska A, Więcek A, Grodzicki T.	Health status of older cancer survivors—results of the PolSenior study.	J Cancer Surviv, 2018; 12(3):326-333	4.074	SOCIAL ISSUES	3 of 40	1
18	Gogler-Piglowska A, Klarzyńska K, Sojka DR, Habryka A, Głowala-Kosińska M, **Herok M**, Kryj M, Halczok M, Krawczyk Z, Scieglinska D.	Novel role for the testis-enriched HSPA2 protein in regulating epidermal keratinocyte differentiation.	J Cell Physiol. 2018 Mar;233(3):2629-2644	3.830	PHYSIOLOGY	13 of 83	1
19	Rewiuk K, Wizner B, Klich-Rączka A, Więcek A, **Mossakowska M**, Chudek J, **Szybalska A**, Broczek K, Zdrojewski T, Grodzicki T.	Atrial fibrillation independently linked with depression in community-dwellingolder population. Results from the nationwide PolSenior project.	Exp Gerontol, 2018; 112:88-91	3.533	GERIATRICS & GERONTOLOGY	19 of 53	2
20	Wyskida M, Owczarek A, **Szybalska A**, Brzozowska A, Szczerbowska I, Wieczorowska-Tobis K, Puzianowska-Kuźnicka M, Franek E, **Mossakowska M**, Grodzicki T, Więcek A, Olszanecka-Glinianowicz M, Chudek J.	Socio-economic determinants of vitamin D deficiency in the older Polish population: results from the PolSenior study.	Public Health Nutr, 2018; 21(11):1995-2003	3.050	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	62 of 181	2
21	Mróz TL, Eves-van den Akker S, Bernat A, Skarzyńska A, **Pryszcz L**, Olberg M, Havey MJ, Bartoszewski G.	Transcriptome Analyses of Mosaic (MSC) Mitochondrial Mutants of Cucumber in a Highly Inbred Nuclear Background.	G3 (Bethesda), 2018; 8(3):953-965	3.048	GENETICS & HEREDITY	82 of 171	2
22	Mazur M, Bartoszewicz A, Dymek B, Salamon M, Andryianau G, Kowalski M, Olejniczak S, Matyszewski K, Pluta E, Borek B, **Stefaniak F**, Zagozdzon A, Mazurkiewicz M, Koralewski R, Czestkowski W, Piotrowicz M, Niedziejko P, Gruza MM, Dzwonek K, Golebiowski A, Golab J, Olczak J.	Discovery of selective, orally bioavailable inhibitor of mouse chitotriosidase.	Bioorg Med Chem Lett, 2018; 28(3):310-314	2.371	CHEMISTRY, ORGANIC	22 of 57	2
23	Majerczyk M, Kocelak P, Choręza P, Arabzada H, Owczarek AJ, **Bożentowicz-Wikarek M**, Brzozowska A, **Szybalska A**, Puzianowska-Kuźnicka M, Grodzicki T, Więcek A, Olszanecka-Glinianowicz M, Chudek J.	Components of metabolic syndrome in relation to plasma levels of retinol binding protein 4 (RBP4) in a cohort of people aged 65 years and older.	J Endocrinol Invest, 2018; 41(10):1211-1219	2.346	ENDOCRINOLOGY & METABOLISM	64 of 142	2

24	Styszynski A, **Mossakowska M**, Chudek J, Puzianowska-Kuznicka M, Klich-Raczka A, Neumann-Podczaska A, **Szybalska A**, Wieczorowska-Tobis K.	Prevalence of anemia in relation to socio-economic factors in elderly Polish population: the results of PolSenior study.	J Physiol Pharmacol, 2018; 69(1):75-81	2.279	PHYSIOLOGY	44 of 83	3
25	De Assis GG, **Gasanov EV**, de Sousa MBC, Kozacz A, Murawska-Cialowicz E.	Brain derived neutrophic factor, a link of aerobic metabolism to neuroplasticity.	J Physiol Pharmacol, 2018; 69(3):351-358	2.279	PHYSIOLOGY	44 of 83	3
26	Majerczyk M, Choręza P, Mizia-Stec K, Bożentowicz-Wikarek M, Brzozowska A, Arabzada H, Owczarek AJ, **Szybalska A**, Grodzicki T, Więcek A, Olszanecka-Glinianowicz M, Chudek J.	Plasma Level of Retinol-Binding Protein 4, N-Terminal proBNP and Renal Function in Older Patients Hospitalized for Heart Failure.	Cardiorenal Med, 2018; 8(3):237-248	2.179	UROLOGY & NEPHROLOGY	33 of 76	2
27	Holko P, Kawalec P, **Mossakowska M**.	Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study.	Eur J Gastroenterol Hepatol, 2018; 30(2):174-180	2.087	GASTROENTEROLOGY & HEPATOLOGY	62 of 80	4
28	Gutmajster E, Chudek J, Augusciak-Duma A, Szwed M, **Szybalska A, Mossakowska M**, Puzianowska-Kuznicka M, Wiecek A, Sieron AL.	Possible association of the TERT promoter polymorphisms rs2735940, rs7712562 and rs2853669 with diabetes mellitus in obese elderly Polish population: results from the national PolSenior study.	J Appl Genet, 2018; 59(3):291-299	1.925	GENETICS & HEREDITY	125 of 171	3
29	Kocełak P, Owczarek A, Bożentowicz-Wikarek M, Brzozowska A, **Mossakowska M**, Grodzicki T, Więcek A, Chudek J, Olszanecka-Glinianowicz M.	Plasma concentration of Retinol Binding Protein 4 (RBP4) in relation to nutritional status and kidney function in older population of PolSenior Study.	Adv Med Sci, 2018; 63(2):323-328	1.681	MEDICINE, RESEARCH & EXPERIMENTAL	84 of 133	3
30	Mehr K, Olszanecka-Glinianowicz M, Chudek J, **Szybalska A, Mossakowska M**, Zejda J, Wieczorowska-Tobis K, Grodzicki T, Piotrowski P.	Dental status in the Polish senior population and its correlates-Results of the national survey PolSenior.	Gerodontology, 2018; 35(4):398-406	1.603	GERIATRICS & GERONTOLOGY	42 of 53	4
31	Kuzniewska B, Sadowski K, Urbanska K, Urbanska M, Kotulska K, **Liszewska E**, Grajkowska W, Jóźwiak S, Dziembowska M.	The level of microRNA 21 is upregulated by rapamycin in serum of tuberous sclerosis complex patients and subependymal giant cell astrocytoma (SEGA)-derived cell cultures.	Folia Neuropathol, 2018; 56(3):167-174	1.330	NEUROSCIENCES	235 of 261	4
32	Bizzarri M, Cassanelli S, **Pryszcz LP**, Gawor J, Gromadka R, Solieri L.	Draft Genome Sequences of the Highly Halotolerant Strain Zygosaccharomyces rouxii ATCC 42981 and the Novel Allodiploid Strain Zygosaccharomyces sapae ATB301T Obtained Using the MinION Platform.	Microbiol Resour Announc, 2018; 7(4) pii: e00874-18	-	-	-	-

Grants

TOTAL NO OF GRANTS IMPLEMENTED IN 2018: 64
TOTAL FUNDING FROM GRANTS IMPLEMENTED IN 2018: 104 810 692 PLN

EU HORIZON 2020

*Number of projects **5***
*Funding **10 495 328 PLN***

- **ERA Chairs** MOSaIC "Molecular Signaling in Health and Disease - Interdisciplinary Centre of Excellence" (810425); 2 498 887,50 EUR; 2018-2023; **J. Kuźnicki**
- **VERTIGO STARTS** epiMimesis "Epizode V: Shifting Identities"; 2018-2019; (supporting role as a producer; grant coordinated by Prof. Hoffmann from the University of the Arts in Poznań); **J.M. Bujnicki**

COST

- EPITRAN "European Epitranscriptomics Network" (CA16120); 2017-2021; **J.M. Bujnicki, E. Purta**
- MOBIEU "Between Atom and Cell: Integrating Molecular Biophysics Approaches for Biology and Healthcare" (CA15126); 2016-2020; **K. Skowronek, R. Szczepanowski**
- IONCHAN-IMMUNRESPON "Ion Channels and Immune Response toward a global understanding of immune cell physiology and for new therapeutic approaches" (BM1406); 2015-2019; **J. Kuźnicki, Ł. Majewski**

EU 7TH FRAMEWORK PROGRAMME

*Number of projects **1***
*Funding **4 083 349 PLN***

Collaborative Project

- EPISTOP "Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex" (602391); 774 818 EUR; matching funds 829 113 PLN; 2013-2018; **J. Jaworski**

INTERNATIONAL FUNDS

*Number of projects **2***
*Funding **3 999 854 PLN***

- **Wellcome Trust International Senior Research Fellowship** "Structural and Biochemical studies of Holliday junction resolution" (0988022); 3 369 854 PLN; 2013-2018; **M. Nowotny**
- **EMBO Installation Grant** (3913); 150 000 EUR, 2018-2021; **W. Pokrzywa**

FOUNDATION FOR POLISH SCIENCE (EU STRUCTURAL FUNDS)

*Number of projects **9***
*Funding **25 908 997 PLN***

- SG OP 4.4. **TEAM** "Molecular mechanism of dendritic arbor stability and its relation to mood disorders" (POIR.04.04.00-00-5CBE/17-00); 3 515 735 PLN; 2018-2021; **J. Jaworski**
- SG OP 4.4. **TEAM** "The interplay between epigenomics and DNA repair" (POIR.04.04.00-00-5D81/17-00); 3 491 914 PLN; 2018-2021; **M. Bochtler**
- SG OP 4.4. **TEAM** "Structural and biochemical studies of the mechanism of LINE-1 retrotransposition and hepadnaviral replication" (POIR.04.04.00-00-20E7/16-00); 3 690 834 PLN; 2017-2020; **M. Nowotny**
- SG OP 4.4. **TEAM** "Cellular consequences of endosomal dysfunction for proteostasis, metabolism and cancer biology" (POIR.04.04.00-00-20CE/16-00); 3 497 520 PLN; 2017-2020; **M. Miączyńska**
- SG OP 4.4. **TEAM** "Modeling of dynamic interactions between RNA and small molecules and its practical applications" (POIR.04.04.00-00-3CF0/16-00); 3 449 541 PLN; 2017-2020; **J.M. Bujnicki**
- SG OP 4.4. **TEAM-TECH** "INFECTLESS New generation of antibacterial wound dressing" (POIR.04.04.00-00-3D8D/16-00); 3 463 780 PLN; 2017-2020; **I. Sabała**
- SG OP 4.4. **FIRST TEAM** "The regulation of methionine metabolism by the ubiquitin-proteasome system: CHIPed supervision of the methylation potential" (POIR.04.04.00-00-5EAB/18-00); 1 999 823 PLN; 2018-2021; **W. Pokrzywa**
- SG OP 4.4. **FIRST TEAM** "Genomics dissection of the heart pacemaker in zebrafish" (POIR.04.04.00-00-1AF0/16-00); 1 999 880 PLN; 2017-2019; **C.L. Winata**
- SG OP 4.4. **HOMING** "Role of ESCRT-I protein complex in amino acid and lipid metabolism in the context of erythropoiesis" (POIR.04.04.00-00-1C54/16-00); 799 970 PLN; 2017-2018; **J. Cendrowski**

NATIONAL CENTRE FOR RESEARCH AND DEVELOPMENT

Number of projects ***3***
Funding ***6 899 620 PLN***

- **STRATEGMED** (acronym EPIMARKER) "Application of novel diagnostic and therapeutical methods in epilepsy and neurodevelopmental abnormalities in children based on the clinical and cellular model of mTOR dependent epilepsy (306306); 3 088 120 PLN (total grant budget: 16 847 247 PLN); 2017-2020; **J. Jaworski** (partner); Coordinator: Medical University of Warsaw
- **STRATEGMED** (acronym DIMUNO) "Development of new cancer therapies based on selective antitumor immunomodulators" (265503); 982 500 PLN (total grant budget: 31 929 500 PLN); 2015-2018; **M. Nowotny** (partner); Coordinator: OncoArendi Therapeutics
- **Applied Research Programme (PBS)** "Development of new biotechnology products based on innovative technique of ribonucleic acid cleavage" (245550); 2 829 000 PLN (total grant budget: 3 316 441 PLN); 2015-2018, Coordinator: **J.M. Bujnicki**

NATIONAL SCIENCE CENTRE

Number of projects ***42***
Funding ***51 223 565 PLN***

MAESTRO

- "Integrative modeling and structure determination of macromolecular complexes comprising RNA and proteins" (UMO-2017/26/A NZ1/01083); 3 500 000 PLN; 2018-2023; **J. M. Bujnicki**
- "Structural and mechanistic studies of bacterial DNA repair" (UMO-2017/26/A/NZ1/01098); 4 228 500 PLN; 2018-2023; **M. Nowotny**
- "Molecular mechanisms of pro-survival processes in breast cancer" (2012/06/A/NZ1/00089); 3 000 000 PLN; 2013-2019; **M. Żylicz**
- "Transgenic mice with elevated basal level of calcium ions in neurons as a model of aged-induced neurodegeneration of sporadic Alzheimer's disease" (2011/02/A/NZ3/00144); 2 989 800 PLN; 2012-2019; **J. Kuźnicki**
- "Structural RNomics" (2012/04/A/NZ2/00455); 3 000 000 PLN; 2012-2018; **J.M. Bujnicki**
- "New functions of endocytic proteins in transcriptional regulation" (2011/02/A/NZ3/00149) 2 875 000 PLN; 2012-2018; **M. Miączyńska**

POLONEZ

- "Deciphering BMP6 regulatory mechanisms using CRISPR/Cas9-based screening approach" (2015/19/P/NZ2/03278); 893 104 PLN; 2017-2018; **K. Mleczko-Sanecka**
- "Deciphering the role of RNA editing in zebrafish development" (2015/19/P/NZ2/03655); 921 064 PLN; 2017-2018; **L. Pryszcz**
- "Genomic profiling of zebrafish cardiac pacemaker cells" (2015/19/P/NZ3/03613); 921 064 PLN; 2016-2018; **R. Minhas**

SYMFONIA

- "Mitochondrial RNA decay and surveillance – comprehensive interdisciplinary studies" (2014/12/W/NZ1/00463); 2 953 248 PLN (total grant budget: 6 879 968 PLN); 2014-2019; **M. Nowotny**

SONATA BIS

- "Role of Rap proteins in regulation of mTOR function" (2012/07/E/NZ3/00503); 1 500 000 PLN; 2013-2018; **J. Jaworski**

HARMONIA

- "Structural biology of mixed lineage leukemia (MLL) proteins" (2014/14/M/NZ5/00558); 1 255 000 PLN; 2015-2018; **M. Bochtler**

DAINA: POLISH-LITHUANIAN FUNDING INITIATIVE

- "CRISPR tools for the study of embryonic development in zebrafish" (2017/27/L/NZ2/03234); 1 634 500 PLN; 2018-2021; **M. Bochtler**; project partner: **G.Tamulaitis** Vilnius University, Lithuania

OPUS

- "Role of TBC1D5 phosphorylation in neurodevelopment and TSC-related cell pathology" (UMO-2017/27/B/NZ3/01358); 1 795 700 PLN; 2018-2021; **J. Jaworski**
- "Development of new methods for designing RNA molecules that fold into desired spatial structures and their use for development of new functional RNAs and for prediction of noncoding RNAs in transcriptome sequences" (UMO-2017/25/B/NZ2/01294): 1 494 250 PLN; 2018-2021; **J.M. Bujnicki**
- "Enabling routine and reliable analysis of transport tunnels in proteins" (2017/25/B/NZ1/01307); 1 375 050 PLN; 2018-2021; **J. Brezovsky**
- "Exploring Baltic Sea cyanobacteria for small-molecule inhibitors of microRNA function" (2017/25/B/NZ9/00202); 27 000 PLN (total grant budget: 1 410 100 PLN); 2018-2021; **F. Stefaniak** (partner); Coordinator: University of Warmia and Mazury in Olsztyn
- "mTOR kinase impact on cellular functions of selected molecular motors" (2016/21/B/NZ3/03639); 1 336 250 PLN; 2017-2020; **J. Jaworski**
- "Finding novel determinants of the brain ventricular system" (2016/21/B/NZ3/00354); 1 294 885 PLN; 2017-2020; **V. Korzh**
- "Biochemical and structural studies of retroviral reverse transcriptases evolution" (2016/21/B/NZ1/02757); 1 145 000 PLN; 2017-2020; **E. Nowak**
- "The role of E3 ligase complexes in integration of protein homeostasis and aging" (2016/23/B/NZ3/00753); 1 116 875 PLN; 2017-2020; **W. Pokrzywa**
- "The impact of intracellular distribution and endocytic transport of lymphotoxin beta receptor (LTbetaR) on its signalling" (2016/21/B/NZ3/03637); 996 125 PLN; 2017-2020; **M. Banach-Orłowska**

- "A coarse-grained method for RNA 3D structure modeling, with emphasis on noncanonical base pairing" (2016/23/B/ST6/03433); 741 250 PLN; 2017-2020; **M. Boniecki**
- "Role of STIM2 isoforms in regulation of neuronal calcium channels in *Danio rerio*" (2016/23/B/NZ3/03142); 2 085 031 PLN; 2017-2020; **J. Kuźnicki**
- "Identification of genes controlling brain development through genomic analysis of patients" (2015/19/B/NZ2/01824); 162 960 PLN (total grant budget: 1 539 596 PLN); 2016-2019; **C.L. Winata** (partner); Coordinator: Institute of Mother and Child
- "New 5-hydroxymethylcytosine binding proteins" (2014/13/B/NZ1/03991); 1 283 750 PLN; 2015-2019; **M. Bochtler**
- "Elucidating the gene regulatory network of zebrafish heart development using genomics" (2014/13/B/NZ2/03863); 955 500 PLN; 2015-2018; **C.L. Winata**

SONATA

- "Characterizing the functions and molecular mechanisms of VPS4B action in biology of colorectal cancer (CRC) cells and in CRC pathogenesis" (2016/21/D/NZ3/00637); 791 850 PLN; 2017-2020; **E. Szymańska**
- "Role of Tollip protein in embryonic development and protein homeostasis in the model of zebrafish (*Danio rerio*)" (2016/21/D/NZ4/00494); 583 750 PLN; 2017-2020; **L. Wolińska-Nizioł**
- "Uncovering the molecular mechanisms of heart regeneration in zebrafish through profiling of contributing genomic factors" (2016/21/D/NZ2/03843); 556 708 PLN; 2017-2020; **K. Nieścierowicz**
- "Endocytosis of AXL receptor and its role in AXL-mediated signaling" (2015/19/B/NZ3/03270); 762 929 PLN; 2016-2019; **D.P. Zdżalik-Bielecka**
- "The role of Zebrafish mTOR in neuronal development in vivo as a key regulator of neuronal circuit formation" (2015/17/D/NZ3/03735); 689 000 PLN; 2016-2019; **J. Zmorzyńska**
- "Functional Characterization of Non-Collagenous Extracellular Matrix Proteins as a Potential Molecular Target and Novel Biomarker of Liver Fibrosis" (2014/15/D/NZ5/03421); 541 875 PLN; 2015-2019; **M. Pawlak**
- "Modeling 3D structures and dynamics of RNA complexes with metal ions, with particular emphasis on the formation of non-canonical base pairs: extension of the SimRNA coarse-grained model towards hish-resolution" (2015/17/D/NZ1/01560); 465 400 PLN; 2016-2019; **D. Niedziałek**
- "Modulation of mitochondrial calcium traffic in pink1 mutant Zebrafish model of Parkinson's disease" (2014/15/D/NZ3/05176); 583 437 PLN; 2015-2018; **S. Soman**
- "Role of CacyBP/SIP in the dysregulation of beta-catenin ubiquitination in YAC128 mouse model of Huntington's disease" (2014/15/D/NZ3/05181); 650 000 PLN; 2015-2018; **M. Czeredys**
- "Patient-specific iPS cells as a novel approach to study pathophysiology of mTOR related neurodevelopmental disorders" (2013/11/D/NZ3/01079); 700 000 PLN; 2014-2018; **E. Liszewska**
- "The contribution of STIM proteins and the role of Store Operated Calcium Entry (SOCE) in calcium homeostasis of neurons" (2011/01/D/NZ3/02051); 684 000 PLN; 2011-2018; **J. Gruszczyńska-Biegała**

PRELUDIUM

- "The role of mu2-adaptin serine 45 and serine 309 phosphorylation in clathrin mediated endocytosis." (2017/25/N/NZ3/01280); 120 000 PLN; 2018-2020; **A. Tempes**
- "Is endocytosis disrupted in tuberous sclerosis complex? Novel studies on human neural stem cells" (2016/23/N/NZ3/00108); 100 000 PLN; 2017-2019; **A. Kościelny**

MINIATURA

- "Photoswitchable Ligands for Riboswitches" (2018/02/XNZ1/01468); 21 670 PLN; 2018-2019; **F. Stefaniak**
- "The influence of surface net charge on the activity of new peptidoglycan hydrolases from Staphylococcus pettenkoferi" (2017/01/XNZ1/00512); 47 740 PLN; 2017-2018; **E. Jagielska**

POLISH NATIONAL AGENCY FOR ACADEMIC EXCHANGE

Number of projects ***1***
Funding ***2 000 000 PLN***

- **International Academic Partnerships** "Molecular basis of enzyme specificity and applications" (PPI/APM/2018/1/00034/U/001); 2 000 000 PLN; 2018-2020; **M. Bochtler, I. Sabała**

MINISTRY OF SCIENCE AND HIGHER EDUCATION

Number of projects ***1***
Funding ***199 980 PLN***

- **Diamond Grant** "Elucidating the mechanism of translational control of maternal transcripts through cytoplasmic polyadenylation" (DI2014 008644); 199 980 PLN; 2015-2019; **M. Łapiński**

MOlecular Signaling in Health and Disease - Interdisciplinary Centre of Excellence

BASIC FACTS

Project title: **MOlecular Signaling in Health and Disease - Interdisciplinary Centre of Excellence**

Project acronym: **MOSaIC**

Project implementation period: **1 November 2018 - 31 October 2023**

Granted amount: **2 498 887.50 EUR**

Referenced call: **H2020-WIDESPREAD-03-2017**

MOSAIC MANAGEMENT CHART

CONCEPT AND OBJECTIVES

The main concept of this project is to create at IIMCB the **Interdisciplinary Centre of Excellence in Molecular Signaling in Health and Disease (MOSaIC)**. We will establish a new research group that is headed by an outstanding principal investigator. This principal investigator will complement and strengthen the current research objectives at IIMCB and influence structural changes to conduct responsible research and achieve effective science management.

MOSaIC has five objectives. The first objective is to **recruit an ERA Chair Group Leader** and affiliates in an open process that involves a set of incentives for the successful candidate to establish an excellent research group. The second objective is to **augment scientific research and innovation at IIMCB and in the surrounding region** through the work of the ERA Chair Group Leader in molecular signaling, a field with great promise for medical advancements. The third and fourth objectives involve **structural improvements in science management and consolidated HR activities** to develop a research environment that meets the highest international standards, including those set forth by the EU Charter and Code. The fifth objective is to **achieve widespread recognition of MOSaIC and IIMCB among national and European stakeholders through dissemination and communication activities.**

Thanks to MOSaIC, IIMCB scientists will lead **innovative and internationally competitive research within an environment of exceptional organizational standards and support**. They will engage in European partnerships, and their projects will lead to practical inventions.

WP 1. Recruitment of the ERA Chair Group Leader and new group members

Leader:
Marcin Nowotny, Head of Laboratory of Protein Structure

For this project to meet its aims, we need to recruit an outstanding mid-career scientist with proven leadership experience for the Senior Group Leader position. The ERA Chair Group Leader will be given the best conditions for research, including optimal laboratory and office space, free access to equipment, and additional benefits. Once recruited, the new Group Leader will autonomously build his or her own research group. The recruitment process is coordinated by Marcin Nowotny. It involves active participation of the IIMCB International Advisory Board and Head of the HR Unit. The latter will also thoroughly support the ERA Chair Group Leader in the recruitment of new laboratory members.

ACTIVITIES IN 2018

We began the recruitment process in July 2018, with the announcement of the open competition for the ERA Chair Group Leader position. The job offer was widely advertised in the most prestigious job portals, including Euraxess, Naturejobs, Science, and the Polish Ministry for Science and Higher Education, as well as in social media (Facebook and Twitter) and through networks of our scientists' and IAB members' contacts. Overall, we disseminated the job announcement through more than 60 different modes. As of the deadline of October 31, 2018, we received 25 applications. Following their formal scrutiny, 18 complete candidatures were sent to the IAB Selection Committee for scientific selection. The IAB shortlisted four candidates by the end of 2018, who were then invited to an interview on March 21, 2019.

WP 2. Strengthening scientific and innovation potential of IIMCB and the surrounding region

Leader:
ERA Chair Group Leader

To boost IIMCB research and innovation, increase its competitiveness, and stay connected with partners across Europe, the ERA Chair Group Leader and his or her group will generate results of their own research and contribute to the overall positioning of IIMCB within the scientific, local, regional, and European landscape. For the scientific functioning of the new group (especially in the initial phase), the ERA Chair Group Leader will be supported by Dr. Nowotny. All formal, organizational, and financial arrangements will be facilitated by various administrative units, including the Grants Office, Scientific Coordination, Accounting, Human Resources, Public Relations, and Information Technology.

WP 3. Structural changes for effective science management at IIMCB

Leader:
Urszula Białek-Wyrzykowska, Deputy Director for Development

To support research and innovation at IIMCB, we continually improve specific internal policies by expanding or adopting them according to national and European recommendations, including ERA priorities. The structural changes cover three distinct areas: good scientific practices (Open Access, Open Data Management, ethics), establishment of IIMCB doctoral school, and IPR management. These structural changes fall under the responsibility of Urszula Białek-Wyrzykowska, Deputy Director for Development and WP3 Leader. She is assisted by experts from the Scientific Coordination Unit, Agnieszka Ziemka and Katarzyna Marszałek, and the Institute's IPR manager. A key element will be conceptual input and advice on the implementation of WP3 tasks from the ERA Chair Group Leader.

ACTIVITIES NOV-DEC 2018

Because of the major changes in Polish legislation (new 2.0 Act), every effort in WP3 in 2018 was focused on researching opportunities for IIMCB to become a member of doctoral school consortia. Urszula Wyrzykowska and Katarzyna Marszałek participated in relevant training, and a lawyer was commissioned to professionally analyze possibilities. Following the lawyer's advice, IIMCB applied to the Polish Central Commission for Degrees and Titles for the right to confer a doctoral degree. This is the first step for IIMCB to open a doctoral school in cooperation with other scientific institutions.

WP 4. Structural changes for more effective implementation of EU C&C principles

Leader:
Katarzyna Fiedorowicz, Head of Human Resources Unit

We enhance the HR Unit. To implement HR-related activities, including the EU Charter & Code principles, professionally and systematically, we are developing the following activities: elaborate the HR Strategy for IIMCB, assist scientists in the recruitment process, organize career development training for IIMCB employees, support foreign employees during their stay in Poland, implement procedures for efficient conflict resolution, and approach gender equality and equal opportunity issues. WP4 is led by Katarzyna Fiedorowicz, Head of the HR Unit.

ACTIVITIES NOV-DEC 2018

To effectively implement these ambitious assignments, Katarzyna Fiedorowicz was recruited in July 2018, before the MOSaIC was initiated. Ms. Fiedorowicz consolidated the HR Unit team of six personnel. Her first tasks included the recruitment and division of assignments among team members, the analysis and improvement of HR-related internal documentation, and establishing strategic goals for the proper implementation of WP4. Fiedorowicz also actively participated in recruitment of the ERA Chair Group Leader by ensuring that the recruitment process adhered to the best standards.

WP 5. Strengthening MOSaIC's recognition among national and European stakeholders

Leader:
Daria Goś, Senior PR Specialist

Dissemination and communication activities are indispensable elements that maximize the impact of MOSaIC's achievements. We explore various means of dissemination and communication and will target numerous communities. WP5 tasks include the dissemination of MOSaIC results by the ERA Chair Group Leader and group members to scientists and potential business partners, the dissemination of results of structural improvements, communicating MOSaIC and its results to different stakeholders, and the elaboration of promotional tools and materials. WP5 is overseen by an experienced PR Manager, Daria Goś.

ACTIVITIES NOV-DEC 2018

These 2 months of 2018 consisted of quite intense communication and dissemination activities. Daria Goś issued press releases to Polish media and governmental institutions and communicated MOSaIC internally. Dorota Libiszowska and Marcin Ogonowski presented the project to the scientific community at Polish NCP information meetings. MOSaIC already has a visual identity and a webpage: www.iimcb.gov.pl/en/research/era-chairs-mosaic. The first Deliverable (D5.7) was submitted to the EU electronic reporting system (selected peer-reviewed publications from the International Institute of Molecular and Cell Biology in Warsaw in high-impact journals in the field of molecular and cell biology).

WP 6. Management

Leader:
Dorota Libiszowska, Head of Grants Office

WP6 involves coordination and management of the project, including monitoring work progress and assessing the implementation of distinct WPs. Management involves a Project Committee, a monitoring body that consists of the Project Coordinator, Project Manager, and WP Leaders. The Project Committee meets regularly to monitor work progress, discuss strategic steps, and respond to unexpected situations. Annual project meetings will involve IAB members who will assess the ways in which the project helps achieve the strategic goals of IIMCB and formulate recommendations for further development. The IAB plays a crucial role in selecting the ERA Chair Group Leader. It will assess the scientific achievements and progress of the new group.

ACTIVITIES NOV-DEC 2018

MOSaIC officially began on November 1, 2018. Immediately before this date, we organized the first Project Committee meeting on October 29, to which we invited IIMCB's directors and all personnel who contribute to implementation of the project. Dorota Libiszowska and Marcin Ogonowski presented the project's concept and objectives and a detailed work plan. Thanks to open and transparent communications, all works to date have been performed smoothly and without delay. The next Project Committee meeting will be held in February 2019.

SCIENTIFIC EVENTS

Scientific Meetings and Lectures

IIMCB's scientific stand promoting the zebrafish model at the Biologists' Night

January 12, 2018

The Biologists' Night was a great opportunity to present zebrafish as a research model to the general public. It was a wonderful opportunity to participate in experiments, listen to lectures, and learn about various fields of biology. This annual event has been held since 2011 at the Faculty of Biology, University of Warsaw.

Talking molecules: the networks that shape the living world

March 19-21, 2018

The 2nd plenary meeting of the Association of Resources for Biophysical Research in Europe–Molecular BioPhysics in Europe (ARBRE-MOBIEU) was sponsored by COST and attended by 140 participants, representing resource laboratories and facilities from 25 different European countries. The scientific sessions focused on molecular interactions, *in vivo* phenomena that are observed from a physics angle, quality control, and multi-approach and multidisciplinary studies.

2nd International FishMed Conference on Zebrafish Research (FishMed2018)

March 25-27, 2018

The purpose of this event was to share the most recent knowledge and findings concerning zebrafish as a model organism. The conference gathered more than 200 participants from 22 countries. The meeting promoted early-stage researchers, for whom dedicated competitive sessions were designed. It was also a great occasion to promote IIMCB's *Be Healthy as a Fish* educational campaign.

Anniversary Symposium

May 17, 2018

This event was held to celebrate the 20th anniversary of IIMCB. The symposium was an opportunity to recall the history and achievements of the Institute over the past 20 years. Scientific lectures were given by Aaron Ciechanover (Technion-Israel Institute of Technology, Israel), Walter Chazin (Vanderbilt University, USA), Anne Spang (University of Basel, Switzerland), and Lilianna Solnica-Krezel (Washington University, USA). The symposium was attended by 233 participants.

IIMCB PhD Students Annual Report Session

June 21 and 28, 2018

These sessions were organized by the IIMCB PhD Students Council, allowing all PhD students from the Institute to present their experimental results. Alicja Kościelny and Marta Kaczmarek received awards for the best presentations.

15th RNase H meeting

September 5-7, 2018

This event was organized by Robert Crouch (National Institutes of Health), Marcin Nowotny (IIMCB), and Małgorzata Figiel (IIMCB). It was attended by 30 participants and focused on ribonuclease H enzymes, including their biology, medical relevance, and potential applications in biotechnology.

Workshop for people with Primary Ciliary Dyskinesia

September 15, 2018

For the fourth time, the Polish Ciliary Dyskinesia Society (which was created at IIMCB in 2011) and IIMCB organized a pro-patient workshop. The meeting was dedicated to respiratory physiotherapy for patients with primary ciliary dyskinesia. The workshop gathered 76 participants, including seven physiotherapists.

3rd edition of Summer School in Bioinformatics & NGS Data Analysis (NGSchool2018)

September 16-23, 2018

IIMCB employee Leszek Pryszcz is a founder of NGSchool initiative. The 2018 edition was attended by 60 participants. This event focused on single-molecule real-time sequencing and personalized medicine.

Evening of Science: Close encounters with proteins

September 28, 2018

This event for youth and adults included lectures and shows. BioCEN also conducted an interactive workshop for children. The meeting was held within the framework of the Festival of Science in Warsaw.

Dr. Filip Stefaniak presenting at the Evening of Science: Close encounters with proteins

Workshop for children at the Evening of Science: Close encounters with proteins

2nd International FishMed Conference on Zebrafish Research

Winners of theFishMed2018 poster awards: Elisa Lidron and Gloria Casas Gemeno

AREBRE-MOBIEU Meeting participants

Regular IIMCB seminars

Magda Konarska (Centre of New Technologies University of Warsaw, University of Warsaw, Poland) ***The less travelled road: the mechanism of the second step of pre-mRNA splicing.*** 18.01.2018

Claudine Kieda (Laboratory of Molecular Oncology, Military Medical Institute, Warsaw, Poland) ***Alleviating hypoxia in the tumor microenvironment by angiogenesis normalization as adjuvant to anticancer therapies.*** 01.02.2018

Kinga Gazda (Laboratory of Neurodegeneration, International Institute of Molecular and Cell Biology in Warsaw, Poland, Institute of Biochemistry and Biophysics PAS, Poland) ***The role of Amyloid Precursor Protein in endoplasmic reticulum Ca2+ homeostasis.*** 15.02.2018

Marcin Nowotny (Laboratory of Protein Structure, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Cryo-EM - the revolution in structural biology.*** 22.02.2018

Michał Mikula (Department of Genetics, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Poland) ***Repositioning oncology oriented drugs for sepsis treatment.*** 01.03.2018

Katarzyna Kisielewska (Laboratory of Molecular and Cell Neurobiology, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Interplay between mTOR kinase and the retromer complex in neuronal development.*** 08.03.2018

Jacek Jaworski (Laboratory of Molecular and Cell Neurobiology, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Molecular neurobiology of mTOR - neurogenesis.*** 15.03.2018

Toshio Yanagida (RIKEN & Osaka University, Japan) ***Single molecule studies of bio-molecular motors.*** 19.03.2018

Hilmar Bading (Department of Neurobiology Interdisciplinary Center for Neurosciences Heidelberg University, Germany) ***The NMDA receptor paradox: survival, death,and paths towards novel neuroprotectivetherapies.*** 22.03.2018

Wojciech Pokrzywa (Laboratory of Protein Metabolism in Development and Aging, International Institute of Molecular and Cell Biology in Warsaw, Poland, Institute for Genetics and CECAD Research Center, University of Cologne, Germany) ***Chaperone-directed ubiquitylation maintains proteostasis at the expense of longevity.*** 29.03.2018

Michał Komorowski (Institute of Fundamental Technological Research Polish Academy of Sciences, Warsaw, Poland) ***Making sense of signaling complexity.*** 05.04.2018

Jacek L. Kolanowski (Department of Molecular Probes and Prodrugs, Institute of Bioorganic Chemistry PAS, Poznan, Poland) ***Small molecule responsive probes for realtime investigation of biochemical analytes in biology.*** 06.04.2018

Mary Anne O´Connell (RNA and Immunity, CEITEC, Brno, Czech Republic) ***ADARs; where the epitranscriptome meetsinnate immunity.*** 13.04.2018

Reiner Wimmer (Institute of Molecular Biotechnology, Austrian Academy of Sciences, Vienna, Austria) ***Stem Cell Models of Human Vascular Diseases.*** 19.04.2018

Wiesława Jarmuszkiewicz (Department of Bioenergetics, Faculty of Biology, Adam Mickiewicz University in Poznań, Poland) ***Impact of temperature and training on skeletal muscle mitochondria.*** 26.04.2018

Michał Rażew (Laboratory of Protein Structure, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Structural studies of the yeast mitochondrial degradosome mtEXO.*** 10.05.2018

Saulius Klimasauskas (Institute of Biotechnology Vilnius University, Lithuania) ***DNA methyltransferases: writers, "readers" and erasers of epigenetic marks.*** 15.05.2018

Michał Hetman (Kentucky Spinal Cord Injury Research Center University of Louisville, Louisville, KY, USA) ***Dysregulated biogenesis of neuronal ribosomes: implications for neurodevelopmental pathologies and beyond.*** 16.05.2018

Edward H. Egelman (Harrison Distinguished Professor Department of Biochemistry & Molecular Genetics University of Virginia, USA) ***Introduction to cryo-EM.*** 23.05.2018

Tomasz Jurkowski (Universität Stuttgart, Institute of Biochemistry, Stuttgart, Germany) ***Synthetic programming of epigenetic states.*** 28.05.2018

Radhan Ramadass (Max Planck Institute for Heart and Lung Research Developmental Genetics Lab, Bad Nauheim, Germany) ***Four Dimensional Cardiac Imaging in Living Zebrafish Embryos.*** 29.05.2018

Fred Dyda (Laboratory of Molecular Biology, National Institute of Diabetes Digestive and Kidney Diabetes, National Institutes of Health, USA) ***Mechanisms of Replicative DNA Transposition.*** 07.06.2018

Yuu Kimata (Department of Genetics, University of Cambridge, United Kingdom) ***Linking Cell Fate to the Cell Cycle: Proteolytic regulation of the centrosome by APC/C-Vihar ensures the oocyte development in Drosophila.*** 14.06.2018

Leos Shivaya Valasek (Institute of Microbiology of the Czech Academy of Sciences, Czech Republic) ***Stop codon readthrough inducing tRNAs and their therapeutic potential.*** 21.06.2018

Jan Rehwinkel (Associate Professor of Innate Immunology Group Leader MRC Human Immunology Unit, University of Oxford, Weatherall Institute of Molecular Medicine, United Kingdom) ***Sensing and Restricting: Innate Immune Control of Virus Infection.*** 05.07.2018

Jakub Godlewski (Assistant Professor, Department of Neurosurgery Brigham and Woman's Hospital, Harvard Medical School, USA) ***Non-coding RNA and tumor heterogeneity.*** 05.09.2018

Miroslav Krepl (Institute of Biophysics of the Czech Academy of Sciences, Czech Republic) ***Simulation studies of protein/nucleic acid complexes – molecular recognition and structural specificity.*** 13.09.2018

Hans Binder (Interdisciplinary Centre for Bioinformatics, University of Leipzig, Germany) ***Molecular landscapes of diseases.*** 14.09.2018

Grzegorz Chojnowski (European Molecular Biology Laboratory Hamburg, Germany) ***Automated building of macromolecular models in X-ray crystallography and cryo-electron microscopy maps.*** 19.09.2018

Joseph Peters (Cornell University, New York, USA) ***Adaptation and control in a highly successful family to transposons.*** 24.09.2018

Wei Yang (NIH Distinguished Investigator, National Institutes of Health, NIDDK, Bethesda, MD, USA) ***Catalytic processes of making and breaking nucleic acid.*** 28.09.2018

Aleksander Grabiec (Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Cracow, Poland) ***Epigenetic regulation in chronic inflammatory diseases: targeting histone acetylation in rheumatoid arthritis and periodontitis.*** 04.10.2018

Dawid Walerych (Lab Leader of Laboratory of Human Disease Multiomics, Mossakowski Medical Research Centre, Polish Academy of Sciences, Poland) ***Oncogenic mutant p53 in cancer - from global approaches to fine details.*** 18.10.2018

Fiona Wardle (Principal Investigator, Muscle Signalling, Randall Division of Cell and Molecular Biophysics, King's College London, United Kingdom) ***Gene regulatory networks in zebrafish germ layer formation.*** 23.10.2018

Henry Löffler-Wirth (Interdisciplinary Centre for Bioinformatics, Leipzig University, Germany) ***Machine learning to disentangle diversity in biodata.*** 26.10.2018

Dominika Nowis (Medical University of Warsaw and Centre of New Technologies University of Warsaw, Poland) ***The role of arginase-1 in the development of antitumor immune.*** 15.11.2018

Krzysztof Chyliński (University of Vienna, Austria) ***CRISPR/Cas9 ribonucleoproteins for efficient genome editing.*** 22.11.2018

Jonas Schwirz (Microscopy Core Facility, Institute of Molecular Biology GmbH, Mainz, Germany) ***Opera Phenix: Project Examples and Data Handling in a Multi-User Environment.*** 27.11.2018

Achim Kirsch and Jürgen Leuck (PerkinElmer) ***From Images to Numbers - High Content Screening with the Opera Phenix.*** 27.11.2018

Ulrike Topf (Institute of Biochemistry and Biophysics Polish Academy of Sciences, Poland) ***Mighty mitochondria: Regulation of protein synthesis in the cell.*** 06.12.2018

IIMCB Annual Report Session
May 25th, 2018, Przypki, Poland

Edward H. Egelman, Department of Biochemistry & Molecular Genetics, University of Virginia, USA, **Keynote Lecture:** ***Cryo-EM of Protein and Nucleoprotein Polymers at Near-atomic Resolution: Evolutionary Insights.***

Bartłomiej Surpeta, Laboratory of Biomolecular Interactions and Transport AMU/IIMCB, ***Design of penicillin G acylase toward degradation of N-acyl-homoserine lactones for effective quorum quenching.***

Paulina Nowak, Laboratory of Cell Biology, ***Synthetic lethality between Vps4A and Vps4B in colorectal cancer (CRC).***

Deepshikha Malik, Laboratory of Protein Structure, ***Structure and mechanism of mitochodrial RNase Rexo2.***

Smijin Soman, Laboratory of Neurodegeneration, ***Neuroprotective effect of MCU inactivation in Zebrafish model of Parkinson's disease.***

Aleksandra Szybalska, PolSenior Project, ***Inequalities in health: a challenge for public health.***

Radosław Pluta, Laboratory of Bioinformatics and Protein Engineering, ***Structural biology of gene control by TUCO and YjdF riboswitches.***

Eugeniusz Tralle, Laboratory of Zebrafish Developmental Genomics, ***Modeling NASH in zebrafish.***

Honorata Czapińska, Laboratory of Structural Biology, ***Modification dependent endonucleases.***

Aniruddha Das, Laboratory of Protein Metabolism in Development and Aging, ***When ligase meets ligase: UFD-2 modulates the activity of the ubiquitin ligase CHN-1.***

Aleksandra Janusz Kamińska, Laboratory of Molecular and Cellular Neurobiology, ***Interplay between Rab11 GTPase and Atg9A at the dendritic spine.***

Dawid Mąkosa, Laboratory of Iron Homeostasis, ***Setting-up tools and approaches to decipher ZIP14 regulatory network.***

Marcin Herok, Department of Molecular Biology, ***p53-independent functions of MDM2 oncogene in DNA damage response in breast cancer cells.***

SUPPORTING YOUNG SCIENTISTS

Supporting Young Scientists

IIMCB has a large and dynamic group of doctoral students - currently 48 - who actively contribute to the research environment and foster links with other institutions at the Ochota Campus. In addition to their research tasks, they participate in one of our partner PhD studies: the School of Molecular Biology Institute of Biochemistry and Biophysics PAS (IBB), the PhD studies of the Nencki Institute of Experimental Biology PAS (Nencki Institute) and the Postgraduate School of Molecular Medicine WUM (SMM).The training programs are tailored to the individual needs of doctoral students and reviewed each year in consultation with the researcher's thesis advisory committee.

There are 49 postdocs at our Institute. Most of these are funded by external grants. The Institute recognizes the career aspirations of its postdoctoral fellows, encourages training, and mentors and supports the individuals in making career choices, including applications for individual fellowships.

The PhD Students and Postdocs Councils are intended to represent all IIMCB young researchers and promote their interests within our Institute and beyond.

Postdoc representatives

Małgorzata Figiel
Almudena Ponce-Salvatierra

PhD Students Council

Gabriela Jędruszewska
Maciej Migdał

PhD Students lab representatives

Justyna Jędrychowska	Kuźnicki Lab
Agata Poświata	Miączyńska Lab
Deepshikha Malik	Nowotny Lab
Karim Abu Nahia	Winata Lab
Sachin Bhausaheb Gadakh	Bujnicki Lab
Anton Slyvka	Bochtler Lab
Magdalena Kędra	Jaworski Lab
Gabriela Jędruszewska	Mleczko-Sanecka Lab
Aniruddha Das	Pokrzywa Lab
Paweł Mitkowski	Auresine

IIMCB representatives at PhD Schools/Studies

IIMCB representative at IBB
Anna Stroynowska-Czerwińska

IIMCB representative at Nencki Institute
Marta Kaczmarek

IIMCB representative at SMM
Justyna Jędrychowska

IIMCB PhD Students representatives (from left: Gabriela Jędruszewska, Paweł Mitkowski, Justyna Jędrychowska, Anton Slyvka, Marta Kaczmarek, Maciej Migdał, Agata Poświata, Sachin Bhausaheb Gadakh, Magdalena Kędra, Anna Stroynowska-Czerwińska)

IIMCB young scientists in action

Maciej Migdał
- Speaker at *RNA-seq data analysis workshop*, Polish Illumina Symposium, Poznań, Poland, October 12, 2018
- Speaker at workshop: *RNA Club Warsaw meets #NGSchool: Vol. 4. RNA-seq data analysis course for biologists*, IIMCB, Warsaw, Poland, May 15, 2018
- Speaker at *2nd International FishMed Conference on Zebrafish Research (FishMed2018)*, Warsaw, Poland, March 25-27, 2018

Karim Abu Nahia
- Co-manager of IIMCB Next Generation Sequencing Facility
- Speaker at *RNA Club Workshop meets #NGSchool: Vol. 4. RNA-seq data analysis course for biologists*, IIMCB, Warsaw, Poland, May 15, 2018
- Laureate of IMS internship scholarship focused on single-cell RNA-seq technique, RIKEN, Yokohama, Japan

Sreedevi Sugunan
- Poster presentation at EMBO/EMBL Symposium: *The Complex Life of RNA*, EMBL, Heidelberg, Germany, October 3-6, 2018

Maciej Łapiński
- Vice-President of Do Science
- Speaker at workshop: *Introduction to Linux, Bioinformatics & NGS, RNA Club meets #NGSchool*, IIMCB, Warsaw, Poland, February 8, 2018
- Poster presentation at EMBO/EMBL Symposium: *The Complex Life of RNA*, EMBL, Heidelberg, Germany, October 3-6, 2018

Anna Stroynowska-Czerwińska
- Short talk in *DNA methylation* session, 3rd Danube Conference on Epigenetics, Budapest, Hungary, October 9-12, 2018
- Oral presentation at VI Conference of Diamond Grant Prizewinners, Kraków, Poland, October 12-14, 2018
- Scholarship for best PhD students, IBB PAS
- Member of Society of Diamond Grant Prizewinners

Norbert Osiński
- Organizer of 7th Intercollegiate Biotechnology Symposium "Symbioza," Warsaw, Poland, May 11-13, 2018

Katarzyna Szafran
- Member of Boost Biotech Poland association

Anton Slyvka
- Scholarship for best PhD students, IBB PAS
- President of Do Science

Karolina Wojciechowska
- Poster prize winner at EMBO practical course *Extracellular Vesicles: From Biology to Biomedical Applications*, Heidelberg, Germany, April 8-14, 2018

Filip Maciąg
- Attended course entitled *Summer School in Bioinformatics 2017*, organized by Wellcome Trust, Cambridge, United Kingdom, June 26-30, 2018

Aniruddha Das
- Participant in EMBO Practical Course on *Characterisation of post-translational modifications in cellular signalling* (EMBO travel grant laureate), Odense, Denmark, April 19-26, 2018

Justyna Jędrychowska
- Co-organizer of *2nd International FishMed Conference on Zebrafish Research (FishMed2018)*, Warsaw, Poland, March 25-27, 2018
- Poster presentation at COST Action BM1406 during conference in Seillac, France, October 8-10, 2018

Magdalena Orłowska
- Attended EMBO Practical Course on *Solution scattering from biological macromolecules*, Hamburg, Germany, November 19-26, 2018

Aleksandra Tempes
- Laureate of Boehringer Ingelheim Fonds Travel Grant for 2-month internship at National Institutes of Health, Bethesda, Maryland, USA, in laboratory headed by Prof. Juan Bonifacino, October-December 2018
- Laureate of 13th National Science Centre (NCN) Preludium competition, November 2018

Magdalena Kędra
- Poster presentation at *11th Zebrafish Disease Models Conference*, Netherlands

Agata Poświata
- 2nd prize winner of best poster at 3rd PhD Student Conference, organized by Nencki Institute of Experimental Biology, Warsaw, Poland, November 11-12, 2018

Etiuda NCN competition winners:
- **Astha** went to Dr. Dan Herschlag laboratory, Stanford University
- **Diana Toczydłowska-Socha** performed internship in Dr. Samie R. Jaffrey laboratory, Weill Cornell Medicine

Diana Toczydłowska-Socha
- Oral presentation at National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Oksana Palchevska
- Active junior member of European Calcium Society and FEBS

Daria Zdżalik-Bielecka
- Poster presentation at EMBO *Cellular signalling and cancer therapy* conference, Cavtat, Croatia, September 14-18, 2018
- Fellowship awarded by The Kosciuszko Foundation for a research stay at Prof. Karen Oegema research group, Department of Cellular and Molecular Medicine, Ludwig Institute for Cancer Research, San Diego, California, USA
- FEBS Short-Term Fellowship for a research stay in Cellular Membrane Dynamics group headed by Prof. Harald Stenmark, Department of Molecular Cell Biology, Institute for Cancer Research, Norwegian Radium Hospital, Oslo, Norway

Sunandan Mukherjee
- Oral presentation at 2nd RNA-Puzzles meeting, IIMCB, Warsaw, Poland, December 6-8, 2018

Nithin Chandran
- Oral presentation at Computational Approaches to RNA Structure and Function, Centro de Ciencias de Benasque Pedro Pascual, Benasque, Spain, July 15-27, 2018
- Oral presentation at 2nd RNA-Puzzles Meeting, IIMCB, Warsaw, Poland, December 6-8, 2018

Pritha Ghosh
- Oral and poster presentation at *Integrative Modelling of Biomolecular Interactions EMBO practical course*, Barcelona Supercomputing Center, Barcelona, Spain, July 2-6, 2018

Annual IIMCB PhD Students Report Session, June 21 and 28, 2018. All 2nd year and above students were asked to prepare presentations on last year's research work. The best presentation prizes went to **Alicja Kościelny** (Laboratory of Molecular and Cellular Neurobiology) and **Marta Kaczmarek** (Laboratory of Cell Biology).

IIMCB PhD student get-togethers: Volleyball Wednesdays, Board Game Mondays, sightseeing and trips, ice skating, trampoline sessions, and dancing classes.

Theses defended in 2018

Karthik Mohanraj, *Transport and degradation of the mitochondrial respiratory chain assembly 1 factor*, supervisor: Agnieszka Chacińska
Piotr Chrościcki, *Cellular mechanisms for effective transport of proteins to mitochondria*, supervisor: Agnieszka Chacińska
Kinga Gazda, *The role of amyloid precursor protein in endoplasmic reticulum Ca^{2+} homeostasis*, supervisor: Jacek Kuźnicki, co-promotor: Tomasz Węgierski
Karolina Mierzejewska, *Structural basis of methylation control of restriction endonucleases*, supervisor: Matthias Bochtler (PhD with honors)
Dawid Głów, *Studies on sequence specificity of MiniIII RNases for double stranded RNA*, supervisor: Krzysztof Skowronek (PhD with honors)
Astha, *RNAs 3D structure determination using hybrid approaches*, supervisor: Janusz M. Bujnicki
Ilona Foik, *Novel inhibitors of RNA methyltransferase responsible for bacterial resistance to antibiotics*, supervisor: Janusz M. Bujnicki
Magdalena Zielińska, *Studies on the mutual regulation of CMTr1 and DHX15, which act as RNA cap methyltransferase and RNA helicase in human*, supervisor: Janusz M. Bujnicki

Training for Talented Youth

Cooperation between the Polish Children's Fund and IIMCB began over a decade ago. IIMCB employees prepare several research events and workshops every year for exceptionally talented children. Research classes in molecular biology mostly attract the Foundation's beneficiaries, for whom the stay at our Institute is often their first real experience with science.

In March 2018, IIMCB organized another training opportunity for talented youth. On the first day, 30 teenagers had the opportunity to listen to lectures and observe the work of the Institute, including the following:

- **Presentation on IIMCB**, Prof. Marta Miączyńska, Head of the Laboratory of Cell Biology
- **Presentation on development of a scientific career at IIMCB**, Dr. Urszula Białek-Wyrzykowska, Deputy Director for Development
- **Presentation on educational programs offered by IIMCB and BioCEN**, Daria Goś, PR Specialist
- **Visiting the Zebrafish Core Facility**,
- **Tour around IIMCB**, Dr. Roman Szczepanowski and Dr. Krzysztof Skowronek, Core Facility

On March 6-9, four talented young people participated in the following activities:

- ***Targeted Genomic Engineering*** by Dr. Małgorzata Perycz and Dr. Joanna Krwawicz, Laboratory of Structural Biology
- ***Genotyping of animals (rodents)***
- ***Preparation of specimens for the dendritic spines analysis*** by Dr. Łukasz Majewski, Laboratory of Neurodegeneration

- ***Microscopic observations of developing zebrafish embryos***
- ***Toxicology test***
- ***Histological stains and phenotype evaluation of zebrafish mutants***
- ***Fish genotyping (DNA preparation, PCR, agarose gel electrophoresis)*** by Dr. Małgorzata Wiweger, Laboratory of Neurodegeneration

Internship program at IIMCB

In 2018, within the innovative MatchBeta career planning platform, IIMCB as the only scientific institution in Poland funded three paid internships: two in the Laboratory of Protein Structure and one in the Laboratory of Iron Homeostasis.

DO SCIENCE!

Do Science! is an informal science club that was formed by PhD students and postdocs from IIMCB and is maintained by young scientists of the Biocentrum Ochota Campus. The Do Science! team seeks to create an opportunity for young scientists to meet, discuss, and learn from the most successful scientists from Poland and abroad in an informal atmosphere where lectures are followed by short career advice sessions and long discussions in a relaxed setting. The Do Science! team also manages the Do Science! SciEvents calendar that aggregates all scientific events that occur on campus and a newsletter that is distributed weekly.
During 5 years of its activities, Do Science! has organized meetings with more than 50 scientists from very diverse fields of biology from all over the world. Do Science! was the inspiration for creating RNA Club Warsaw (www.facebook.com/RNAClubWarsaw/) and Do Science! Poznań (www.facebook.com/DoSciencePoznan/).

Do Science! organized the following meetings in 2018

Jacek Kolanowski, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland

April 6, 2018

Scientific career path

Dr. Jacek Kolanowski is the Head of the Molecular Probes and Prodrug Laboratory at the Institute of Bioorganic Chemistry, Polish Academy of Sciences (Poznań). He is a young principal investigator who returned from his postdoc at the University of Sydney. Dr. Kolanowski's research achievements have numerous applications for monitoring various factors in living systems in both health and disease. He and his colleagues developed fluorescent redox sensors, ion metal sensors, ion biosensors, and sensors for the simultaneous detection of multiple analytes, among others. These tools can be used at the organismal, cellular, and organellar levels. Dr. Kolanowski spoke about his scientific life and how his research perspectives have evolved.

Mary O'Connell, Central European Institute of Technology, Brno, Czech Republic

April 12, 2018

RNA editing/modification

Prof. Mary O'Connell is one of the most renowned scientists in the field of RNA editing. She and her group study adenosine deaminases that act on RNA (ADARs), enzymes that edit double-stranded RNA by deaminating adenosine to inosine. Edited adenosine is read as guanosine by cellular machinery. This allows for an amino-acid substitution in the protein sequence at the mRNA level and very often leads to dramatic changes in the properties of the encoded protein. Her group seeks to understand the biological role of RNA editing using model organisms, such as mice and Drosophila, to study the phenotypical consequences of ADAR overexpression and knockdown. Prof. O'Connell's lecture was an overview of the world of RNA modifications, in which she presented the most important and currently unanswered questions in the field.

Saulius Klimašauskas, Institute of Biotechnology, Vilnius University, Lithuania

May 14, 2018

DNA methylation

Prof. Saulius Klimašauskas, Chief Scientist and Head of the Department of Biological DNA Modification, Institute of Biotechnology, Vilnius University, focuses on many aspects of nucleic acid modifications. He and his coworkers developed advanced chemical and biochemical approaches that revolutionized epigenetic research. They use engineered DNA and RNA methyltransferases and synthetic S-adenosyl-L-methionine analogues to introduce chemically distinguishable groups into DNA or RNA. The basic research that is conducted in Prof. Klimašauskas' laboratory led to the development of robust techniques that are available for routine laboratory use, such as tethered oligonucleotide-primed sequencing (TOP-seq), methyltransferase-directed transfer of activated groups (mTAG), sequence-specific methyltransferase-induced labeling (SMILing), and many others. Prof. Klimašauskas has been an International Research Scholar of the Howard Hughes Medical Institute (1995-2005). He was a JSPS invited professor at Osaka University (2002) and a recipient of an ERC advanced grant (2017). He was elected Fellow of the Royal Society of Chemistry (in 2015) and EMBO member (in 2017). Prof. Klimašauskas' talk was about development of the field of DNA-modifying enzymes for which he was one of the pioneers.

German Demidov, University of Tübingen, Germany

September 3, 2018

Welcome to Pan-Cancer Atlas

German Demidov is a bioinformatician who is currently involved in the Bioinformatics PhD program at the University of Tübingen. He mainly works on human cancers and looks at CNVs and NGS data from WGS/exome-seq. He is excellent at sharing his knowledge and experience and has co-organized summer schools (#NGSchool2016, #NGSchool2017, #NGSchool2018, etc.). His talk was on the challenges of "big data" collection and processing and the useful information that can be extracted from such data. The Pan-Cancer Atlas is a result of the hard work of many wet-lab scientists and bioinformaticians. It explains the genetic/epigenetic background of many cancers and may also have predictive power.

Hans Binder, Interdisciplinary Centre for Bioinformatics, Leipzig University, Germany

September 13, 2018

Our way out of Africa – issues of modern gene bioinformatics

Dr. Hans Binder is the managing director of the Interdisciplinary Centre for Bioinformatics at Leipzig University. His current scientific interests involve the genomic regulation of cell functions. His group develops and applies algorithms and methods to extract relevant biological information from large sets of high-throughput data. They analyze large-scale molecular data (especially DNA, RNA, and Meth Seq) that are generated in patient cohorts, epidemiological collectives, cell-line experiments, and single-cell experiments. Dr. Binder's talk was on the capabilities of advanced bioinformatics in the field of human evolutionary biology.

RNA Club Warsaw

The organization of RNA Club Warsaw meetings was the first activity that was considered when the RNA Club was formed. During the last season and similar to previous years, we arranged three events. They consisted of talks that were given by junior scientists who perform research at the Ochota Campus and short lectures that were given by experts in the RNA field. The idea behind this series of meetings was to present challenging research cases with a chance to consult them with more experienced researchers in the field, to exchange ideas and share knowledge. The scheduled portion of the meetings was usually followed by informal discussions with food and refreshments that were provided for all participants, creating a favorable networking atmosphere.

I

RNA Club Warsaw Meeting I
January 22, 2018

Grzegorz Brzyżek (Instituteof Biochemistry and Biophysics PAS), **Zbigniew Pietras** (Institute of Biochemistry and Biophysics PAS), **Radosław Pluta** (IIMCB), **Marcin Równicki** (Centre of New Technologies), **Adam Mamot** (Centre of New Technologies)

II

RNA Club Warsaw Meeting II
April 17, 2018

Anna Mościcka (University of Warsaw), **Katarzyna Łepeta** (Nencki Institute of Experimental Biology), **Błażej Bagiński** (IIMCB), **Joanna Najmuła** (Institute of Animal Reproduction and Food Research PAS), **Zbigniew Warkocki** (Institute of Biochemistry and Biophysics PAS)

III

RNA Club Warsaw Meeting III
May 24, 2018

Prof. Andrea Rentmeister (University of Münster), **Prof. Tom Grossmann** (Vrije Universiteit Amsterdam), **Prof. Jacek Jemielity** (Centre of New Technologies), **Prof. Janusz Bujnicki** (IIMCB), **Dr. Filip Stefaniak** (IIMCB)

RNA Club Meets #NGSchool

RNA Club Meets #NGSchool was a fruitful collaboration that was initiated last season, mainly between members of two different research groups of the International Institute of Molecular and Cell Biology in Warsaw. The resulting series of workshops were geared toward experimental biologists who have little or no experience in computational studies but would like to broaden their range of analyses. The classes focused on the basics of RNA bioinformatics using freely available software and web-servers. The workshops received favorable attention, with an active group of participants taking part in the entire course. The list of organized meetings with the names of speakers conducting the classes is presented below:

- ***RNA Club Meets #NGSchool 0 (Workshop): Introduction to Linux, Bioinformatics, and NGS*** — February 8, 2018
  Maciej Łapiński (IIMCB), Leszek Pryszcz (IIMCB)
- ***RNA Club Meets #NGSchool I (Workshop): De novo genome/transcriptome assembly and annotation*** — March 8, 2018
  Magdalena Płecha (UW), Leszek Pryszcz (IIMCB)
- ***RNA Club Meets #NGSchool II (Workshop): ChIP-seq data analysis*** — April 9, 2018
  Maciej Łapiński (IIMCB)
- ***RNA Club Meets #NGSchool III (Workshop): RNA-seq data analysis course for biologists*** — May 15, 2018
  Karim Abu Nahia (IIMCB), Maciej Migdał (IIMCB), Michał Pawlak (IIMCB)

RNA Puzzles Meeting

The RNA Puzzles Meetings are a combination of workshops and lectures devoted to RNA structure modeling, centered on the RNA Puzzles contest, a CASP-like community-wide exercise to predict RNA 3D structures. The aim of the RNA Puzzles contest is to encourage the RNA structure prediction community to improve the current tools in the form of a competition. The RNA Puzzles Meetings have been initiated by Eric Westhof. The first one was organized by his research group in Strasbourg, and the second – by the Bujnicki laboratory and it was held at IIMCB in Warsaw. The open session of the RNA Puzzles Meeting was co-organized by RNA Club Warsaw. We invited renowned experts in areas related to RNA structure determination, who gave keynote presentations of their fields and their relevance to research activities of the RNA Puzzles community. The list of keynote speakers is presented below:

- ***RNA Puzzles Meeting*** — December 7, 2018
  Prof. Jiri Sponer (CEITEC), Prof. Samuela Pasquali (Paris Descartes University), Prof. Petr Sulc (Arizona State University)

EDUCATION

Centre for Innovative Bioscience Education

Head

Patrycja Dołowy, PhD

Project Manager

Aleksandra Kot-Horodyńska

Laboratory Manager

Aleksandra Olszańska

Coordinator

Karolina Kurzela

The Centre for Innovative Bioscience Education (BioCEN) was established in 2002 by enthusiastic young scientists who recognized the importance of popularizing science among the broader community. Since then, BioCEN has been continuously working to achieve this goal by organizing and conducting educational activities, such as laboratory workshops for elementary and high school students, practical courses for school teachers, scientific training for businesses, open lectures for broader audiences, scientific shows, and picnics for children. We believe that learning the scientific method is key to understanding today's world. The aim of BioCEN is to bridge the gap between science and society by conducting educational activities and popularizing the theme of modern biology. BioCEN could not continue its mission without financial support from the International Institute of Molecular and Cell Biology (IIMCB) in Warsaw, which has been BioCEN's Strategic Sponsor since 2015. In addition to IIMCB's support, BioCEN is also subsidized by the Nencki Institute of Experimental Biology (Polish Academy of Sciences), Institute of Biochemistry and Biophysics (Polish Academy of Sciences), University of Warsaw Faculty of Biology, and BioEducation Foundation.

WORKSHOPS

BioCEN workshops cover various areas of biology and life sciences and appear to be a remedy for a weakness of the Polish education system, namely an insufficient focus on practical and experimental approaches. Therefore, our goal is to cover several scientifically and educationally important topics, such as molecular and cellular biology, histology, immunology, biochemistry, biotechnology, microbiology, biophysics, plant physiology, bionics/bioengineering, and medical sciences. We encourage participating students to take advantage of their creativity while working individually on real-life experiments. This is advantageous because workshops at BioCEN for most students are their only opportunity to perform laboratory work on their own. Notably, over the last 17 years, approximately 40 000 students have had the opportunity to take advantage of the workshops that are offered by BioCEN.

Since April 2018, we have introduced six new workshops. Three workshops were tailored to pupils: physics and biophysics (surface tension, material densities), optics, and environmental microbiology. Two new workshops were tailored to 7th and 8th grade pupils: plant physiology and environmental microbiology. One workshop was tailored to high school students: medical and nutritional microbiology.

We also updated four of our workshops for high school students: Explore your own DNA, Protein fingerprints, Biotechnology of antibodies in clinical practice, and Histology, embryology, and stem cells.

In 2018, BioCEN held 286 workshops based on 31 different topics. More than 7 100 students participated. Creating and conducting the workshops were possible because of five projects (programs) that were co-funded by the Department of Education in Warsaw City Call, coordinated by Aleksandra Kot-Horodyńska.

Because of the location of BioCEN, access is somewhat limited to students who live outside

Warsaw. As such, the BioCEN team is ready to organize and implement laboratory workshops outside its headquarters. We believe this move will be an effective way to increase life science awareness and scientific skills among a wider population and thus will be an important component of our program.

FLYING SCIENCE CAFES AND WORKSHOPS FOR REFUGEES

In collaboration with the Council for the Promotion of the Public Understanding of Science (Polish Academy of Sciences) and SPACES Foundation, we organized science cafes for adults and science workshops for children age 7-12 who are refugees who live in refugee centers in the Mazowieckie and Podlaskie regions in Poland. Two 2-h workshops for children based on biophysics and optics were held in BioCEN's laboratory at Grójecka 93 st. After the workshops, the children received gifts, including two books: one about zebrafish (published by IIMCB) and the other on simple self-made experiments (published by BioCEN), balloons, crayons, and stickers.

INTERNATIONAL COOPERATION

Workshops for international students at the "Where is Europe" conference organized by Rijskuniversiteit Groningen and Jagiellonian University in Cracow

The Head of BioCEN, Patrycja Dołowy, PhD, gave a lecture and organized a workshop for international students about popularizing science and teaching using the scientific method. The aim of the workshop was to learn about the scientific method and how using the experiments in hands-on type of education influence the process of learning

Participation in Science Week in Berlin

BioCEN participated in Science Week in Berlin and the Falling Walls Conference. Science Week is an annual, international gathering that brings people together from the world's most innovative scientific institutions to celebrate science and connect local and international scientific societies with the public. It is dedicated to fostering dialogue between science and society to inspire a deeper understanding of our world. It comprised more than 100 events that were organized by local and international institutions.

PROFESSIONAL TRAINING

Professional training for young scientists of the Polish Academy of Sciences

One of our main goals is to improve the teaching skills of science educators who work at all levels of education. In 2018, BioCEN was involved in professional training for young scientists whose goals include popularizing their experiments and results for the public. The event was organized by the Polish Young Academy of the Polish Academy of Sciences.

17th Educational Symposium for Biology Teachers

This symposium has become one of our most important events. The most recent symposium was held on Saturday, December 1, 2018. During this meeting, biology teachers from all over Poland had the opportunity to receive up-to-date information on frontline discoveries in neuroscience and become more familiar with cutting-edge studies, such as those that were related to the Nobel prizes in Chemistry and Medicine. Moreover, teachers had the unique opportunity to talk to academic researchers in person and create social networks, which has a positive impact on the quality of their teaching. The symposium was organized in cooperation with the Nencki Institute of Experimental Biology, Polish Academy of Sciences, in Warsaw.

Experimental kits and other scientific tools

For those who are unable to take advantage of our workshops, we provide alternatives. BioCEN produces laboratory kits that are commercially available through our website. All of the kits come with the necessary chemicals, dishes, tubes, theoretical summaries, instructions, and protocols that are needed by students to perform a particular experiment either at school or at home. To date, the following experimental kits are available:

- We are studying DNA
- The sweet world of experiments
- Photosynthetic dyes
- A necklace with your own DNA
- Each of these kits come in small and large versions.

We also emphasize the notion of "learning while playing." As such, we also produce high-quality, genuine BioCEN educational board games:

- By the trails of evolution
- Dare to assemble your cell (still in testing)

Especially for teachers, we have lesson scripts and experimental protocols available on our new website. Some of the scripts and protocols have been updated based on the latest science results.

EVENTS

22nd Festival of Science in Warsaw

As in previous years, BioCEN participated in the 22nd Festival of Science; this time, participation occurred in collaboration with the International Institute of Molecular and Cell Biology in Warsaw. We organized and held two 90-min scientific workshops that were related to the Nobel prizes in Chemistry and Medicine, entitled "Close Encounters with Proteins" for children aged 6-13. The children's parents could also listen to the lectures that were given by IIMCB scientists about their research on proteins and their applications.

16th Summer Meetings with Science

The Summer Meetings with Science event has been co-organized for 17 years by the Institute of Oceanology (Polish Academy of Sciences) together with the Institute of Hydro-Engineering (Polish Academy of Sciences) and Baltic Science Festival. Patrycja Dołowy, PhD, lectured at this event for the seventh time. For the first time, she represented BioCEN and spoke to Summer Meetings with Science attendees about BioCEN's activities and goals, which led to further future collaborations.

BIOCEN ANIMATORS AND CO-WORKERS

Important members of the BioCEN team include animators and co-workers without whom the educational activities would not be possible. In 2018, the following individuals collaborated with BioCEN in this capacity: Kryspin Andrzejewski (animator), Tamara Aleksandrzak-Piekarczyk (laboratory support, author of workshops), Patrycja Dołowy (president of the board of the BioEducation Foundation, animator, author of workshops), Maciej Grochowski (laboratory support), Andrzej Gruza (animator), Piotr Horodyński (designer, author of workshops), Weronika Iwaniuk (animator), Rafał Jabłuszewski (animator), Monika Jakubiak (animator), Katarzyna Jędrzejowska (animator), Agnieszka Kamińska (animator, author of workshops), Magdalena Karpińska (animator), Izabela Kern-Zdanowicz (laboratory support, author of workshops), Aleksandra Kot-Horodyńska (project manager, member of the board of the BioEducation Foundation, author of workshops), Maciej Kotliński (member of the board of the BioEducation Foundation, animator), Kinga Lipka (animator), Katarzyna Łepeta (laboratory support, author of workshops), Aleksandra Kowalczyk (animator), Katarzyna Krzyczmonik (animator), Sebastian Kwiatkowski (animator), Paweł Morga (animator), Michał Niziołek (laboratory support), Aleksandra Olszańska (laboratory coordinator since September 1, 2018, animator), Michał Oziębło (animator, author of workshops), Jacek Patryn (head of BioCEN until March 31, 2018, animator, author of workshops), Zuzanna Sobańska (laboratory coordinator from February to August 2018), Kamil Synoradzki (laboratory coordinator from January to February 2018, animator), Barbara Świerczek-Lasek (animator), Jan Maurycy Święcicki (animator), and Michał Wielądek (animator).

Centre for Innovative Bioscience Education (BioCEN) 93 Grójecka Street, 05-077 Warsaw, Poland +48 530 575 050 biocen@iimcb.gov.pl www.biocen.edu.pl

Be Healthy as a Fish educational program

The main character of the Be Healthy as a Fish educational campaign is the zebrafish, which helps scientists find the cause of certain human diseases and discover new-generation therapies and medicines. The program is directed toward children aged 9-12 years old.

Workshop
1035 participants

Book
2800 downloads

Movie
5300 views

WORKSHOP

For the young target audience, the workshop is an opportunity to visit a real scientific institute. During the classes, the participants are introduced to the zebrafish as a model organism that is used in basic and applied research because of its high genetic similarity to humans, transparent embryos, very short reproduction cycle, access to experimental manipulations, large collection of mutant/transgenic lines, and low maintenance cost. Therefore, the zebrafish is an attractive alternative to mammalian *in vivo* models and can be used to implement the "3R" principles (reduction, replacement, and refinement). To empathize with the role of scientists, the students observe 1- to 2-day-old zebrafish embryos under a stereoscopic microscope. They have the opportunity to see the beating heart of a small fish and living brine shrimp (*Artemia*) larvae and rotifers. They learn that zebrafish development is very similar to the embryogenesis of higher vertebrates. In contrast to mammals, zebrafish develop from fertilized, transparent eggs outside the mother's body, which allows scientists to observe the embryogenesis process.

Participants of the workshop learn how much the human body is similar in its genesis and development to the body of a small fish. They learn that when scientists observe the zebrafish, human embryogenesis, and the mechanisms of the human body, various functions can be better understood. By explaining the concept of the homology of genomes, they are shown the importance of animals in the multi-stage process of discovering new drugs and therapies. We also show participants how we breed zebrafish and how we tend to their welfare. We familiarize children with the issues of ethics in research that is performed with animals.

The participants independently investigate water properties by performing colorimetric tests and measuring the pH and hardness of tap water and aquarium water that is used in the facility. Water analyses are supervised by animal caretakers who work at IIMCB. The children are permitted to perform water tests themselves and have the opportunity to ask questions about zebrafish husbandry, fish biology, operation of the fish facility, and other tasks. At the end of the workshop, the students are given the *Be Healthy as a Fish* book and a three-dimensional bookmark with images of zebrafish.

MOVIE

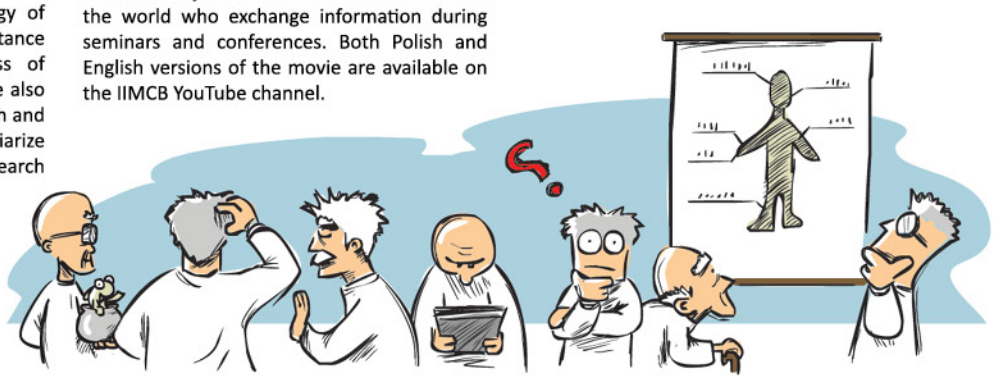
The aim of the movie is to familiarize viewers with IIMCB's facilities and scientific interests and show the everyday work lives of scientists. This 6-min movie is mostly animated. However, part of it shows real images of various locations within the institute (e.g., laboratories, fish facility, office of the Director of IIMCB, and a lecture hall where the workshops are held). The storyline of the animation consists of a humorous tour around the institute that is guided by two cartoon characters: the Professor and a zebrafish. During the tour, the children are told the reason why the zebrafish facility was established, and they can witness the formation of a new international team of scientists. The viewers are informed that science has no borders, and new discoveries result from joint efforts of scientists around the world who exchange information during seminars and conferences. Both Polish and English versions of the movie are available on the IIMCB YouTube channel.

BOOK

The book brings the complex world of science closer to young readers. Because the book is geared toward primary school children with elementary knowledge of life sciences, it is illustrated with cartoons to make the content more interesting for a young audience. Moreover, to help readers absorb the story's message, the book provides engaging assignments. A short glossary defines terms that are used in the book that may be difficult for some readers to understand. Importantly, the factual content was created in consultation with an educational biology expert to ensure that the message of the story is both understandable and inspiring for a young audience.

The book is distributed to all of the participants of the workshop as an invitation to broaden their knowledge beyond the topics that are discussed in their classes. The content of the book was written such that it can be regarded as an independent story from which those who do not participate in the workshops can benefit. The *Be Healthy as a Fish* book can be interesting additional material for teachers to support discussions about the evolution of life, cell biology, heredity, and anatomical similarities between humans and animals.

www.iimcb.gov.pl/en/institute/education/be-healthy-as-a-fish



BE HEALTHY AS A FISH

RESEARCH SUPPORT UNITS

Research Support Units (as of December 31, 2018)

Grants Office

Alexia Danyłow, Specialist

Dorota Libiszowska, Head

Agata Skaruz, Specialist

Marcin Ogonowski, Vice Head

Justyna Szopa, Specialist

Katarzyna Nakielska, Specialist (not in the picture)

HR Unit

Adam Zieliński, Specialist

Monika Nowicka, Senior Specialist

Paulina Okafor, Specialist

Katarzyna Fiedorowicz, Head

Beata Tkacz, Senior Specialist

Agnieszka Faliszewska, Senior Specialist

Monika Domańska-Paśko, Specialist

Administration

Ewa Jack-Górska, Specialist

Andrzej Cudny, Specialist

Dominika Dubicka-Boroch, Senior Specialist

Adam Kucharski, Building Maintenance

Anna Zolnik, Deputy Director for Operations

Mariola Sacharuk, Junior Specialist

Agata Szulim, Specialist

Daria Goś, Senior Specialist

Agnieszka Potęga, Specialist (not in the picture)

Financial and Accounting Unit

Magłorzata Bytner, Senior Specialist

Hanna Iwaniukowicz,
Chief Accounting/Deputy Director for Finance

Agnieszka Kuna, Senior Specialist

Renata Knyziak, Senior Specialist

Scientific Coordination Unit

Katarzyna Marszałek, Senior Specialist

Agnieszka Wagner-Ziemka, Chief Specialist

IT Unit

Łukasz Munio, Specialist

Tomasz Jarzynka, Specialist

Piotr Świsłowski, Senior Specialist

Jakub Skaruz, Specialist

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